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THE AMERICAN REVIEW OF TUBERCULOSIS

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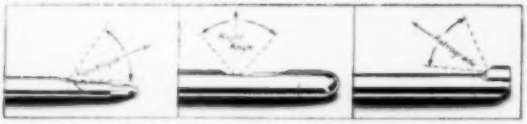

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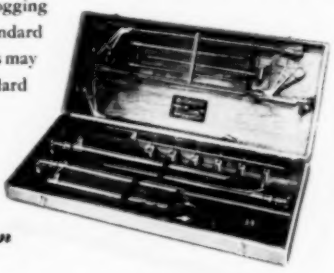

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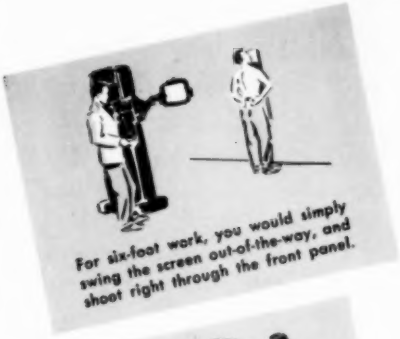

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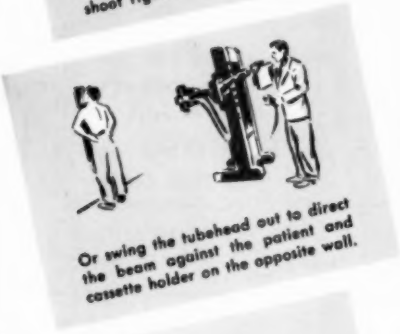

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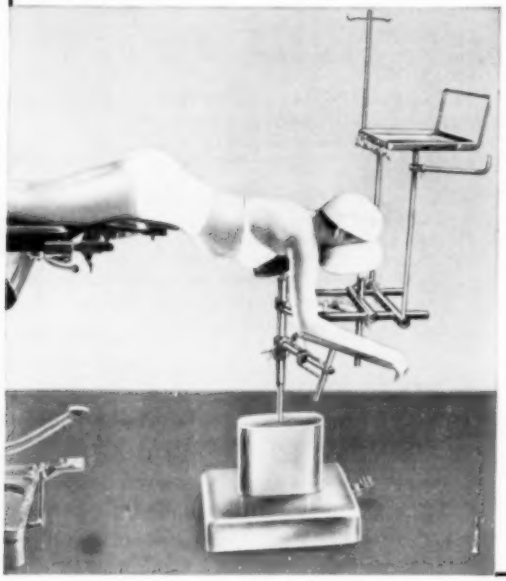

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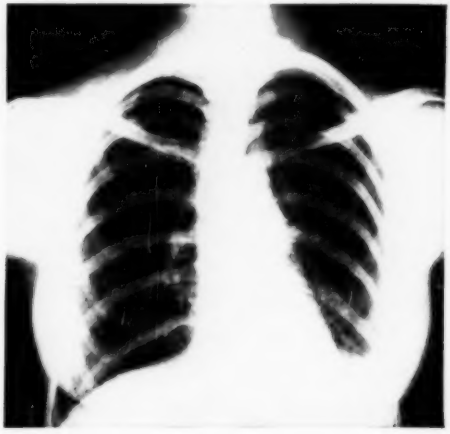

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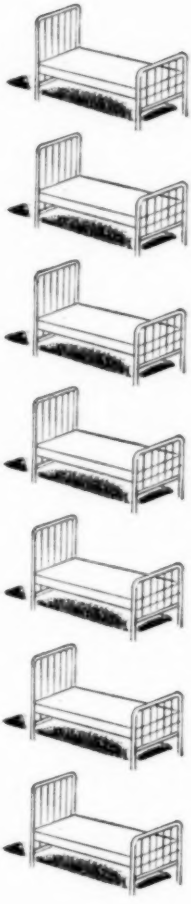

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THE COST OF RESEARCH ON TUBERCULOSIS IN THE UNITED STATES

Analysis of Allocations in 1947–1948

VIRGINIA CAMERON[1]

(Received for publication May 2, 1949)

INTRODUCTION

Within the last ten years important scientific discoveries have led to greatly increased appropriations for research in the United States. Investigations in physico-chemical, medical, and other fields were stimulated and intensified by World War II. Establishment of a National Science Foundation, under the auspices of the Federal Government, has been much discussed in recent years and, in 1947, the President's Scientific Research Board made a survey of research under way at that time, its cost, and the future needs for a well coordinated program of scientific research in the United States.

According to Mr. John R. Steelman, Chairman of the President's Scientific Research Board,

> As a Nation, we should spend each year no less than one per cent of our national income for research and development in the physical and biological sciences, including medicine. . . . Our present national research and development budget amounts to about one-half of one per cent (1). . . . The Nation as a whole invests only around $110 million annually for scientific research and development in medical and allied fields, as contrasted with more than 10 times that amount spent for all other forms of scientific inquiry (2).

Mr. Steelman points out further that

> The challenge of our times is to advance as rapidly as possible the understanding of diseases that still resist the skills of science, to find new and better ways of dealing with diseases for which some therapies are known, and to put this new knowledge effectively to work (2).

Singularly, this statement represents the philosophy of the Committee on Medical Research of the National Tuberculosis Association in the establishment of a medical research program in the fall of 1920. In his presidential address at the annual meeting of the Association in 1921, Dr. Gerald B. Webb reiterated the principles set down by the Committee when he stated that

> We must frankly state our knowledge of the disease, and also the extent of our ignorance regarding tuberculosis, so that we can more wisely guide the efforts made in prevention and cure, and direct research to bring further enlightenment (3).

Stimulated by the findings of the President's Scientific Research Board and by a desire for a more detailed analysis of the cost of investigation in its own field, the Division of Research of the National Tuberculosis Association col-

[1]Medical Research Secretary, American Trudeau Society, Medical Section of the National Tuberculosis Association.

lected information on the amount spent for tuberculosis research in the United States. Data were compiled with the assistance of official and voluntary agencies, universities, foundations, pharmaceutical houses, and firms manufacturing X-ray equipment. Although the fiscal year varies with different organizations, the figures used represent funds reported for a twelve-months' period during 1947–1948.

The survey is not exhaustive, but it is hoped it will present sufficient information to be of some value in future planning. There are many intangibles, the cost of which cannot be accurately reckoned, and the greatest of these is personnel. Services within all of the groups mentioned above, as well as the cost of buildings and their maintenance, which may indirectly increase the cost of tuberculosis research, represent a sum impossible of calculation. Undoubtedly it is of large size.

TYPES OF RESEARCH

Research, according to Mr. Steelman (2), may be categorized as follows: (a) basic, or fundamental research, *i.e.*, theoretical analysis, exploration, or experimentation; (b) background research, *i.e.*, systematic observation, collection, organization, and presentation of facts; (c) applied research, *i.e.*, extension of basic research to the determination of the combined effects of physical laws or generally accepted principles with a view to specific application; and (d) development, *i.e.*, adaptation of research findings to experimental, demonstration, or clinical purposes. This is not a new concept but one which may well bear repeating here.

While "research" in general terms often is assumed to represent investigations of a purely scientific nature, epidemiological, statistical, social, and historical research are of considerable importance in the solution of problems for the control of tuberculosis. The principles set down above can, in most instances, be adapted to apply to these fields.

PRESENT RESEARCH PROGRAM

Official Agencies

Public Health Service

Within the last few years, by far the most extensive program for research in tuberculosis has been that of the Federal Government. Since the establishment of the Tuberculosis Control Division in the United States Public Health Service in 1944, an increasing appropriation of funds for tuberculosis control has been made. It was reported that in the last fiscal year (1947–1948) a sum of $300,000 was allocated to the Field Studies Section of the Division for statistical and epidemiological research, and $43,529 appropriated for the Tuberculosis Evaluation Laboratory, set up within the last few years in Atlanta, Georgia, the primary purpose of which is to standardize laboratory procedures for the detection of tuberculosis.

In the National Institutes of Health, late in 1946, an enlarged program of in-

vestigations was set up, stimulated by early studies of a group of investigators in the American Trudeau Society, Medical Section of the National Tuberculosis Association (4, 5). A Tuberculosis Study Section, composed of specialists in the field, was organized primarily for the purpose of evaluating the effectiveness of streptomycin in the treatment of tuberculosis through establishment of research grants to qualified investigators (6). During the fiscal year 1947–1948, reports show that 31 grants for laboratory and clinical studies were approved, amounting to $589,700. In addition, $250,000 was set aside for the estimated cost of the streptomycin, and $80,000 for fellowships. A Central Coordination and Analysis Office was established to correlate and analyze the findings of the various clinical investigations for an evaluation of the therapeutic value of streptomycin in tuberculosis. In addition to these studies, the Division of Infectious Diseases of the National Institutes of Health continued its investigations of various chemotherapeutic agents and the relation of histoplasmosis to pulmonary calcification, synthesis and testing of commercial compounds and antibiotics, and the synthesis of new drugs and their synergistic action with antibiotics such as streptomycin. For this research approximately $94,800 was budgeted in the above period, according to data received.

The total expenditure reported for the tuberculosis research program of the Public Health Service for the fiscal year 1947–1948 amounted to approximately $1,358,029, with $934,500 devoted to investigations with chemotherapeutic agents.

Department of Agriculture

The Bureau of Animal Industry, United States Department of Agriculture, carried out studies of the tubercle bacillus and other acid-fast organisms affecting bovine and avian species at a reported cost of $26,300 for the 1947–1948 fiscal year.

Department of the Interior

In the United States Department of the Interior, the Office of Indian Affairs stated that $50,795 was allocated in the same period for experimental investigations with BCG in certain segments of the Indian population.

Department of the Army

The Army tuberculosis research program included a study of minimal tuberculosis in a group of 1,100 cases at Fitzsimons General Hospital, with an annual budget of $28,552, exclusive of the cost for military personnel. In addition, the cost of streptomycin for experimental investigations was $160,200. Studies of the relation of nutrition to tuberculosis in the Medical Nutrition Laboratory at Chicago were made at a cost of $9,000. Administrative expense in the central office for personnel engaged full time in tuberculosis research, as well as advisory service procured from the National Research Council, amounted to $30,000.

In accordance with the foregoing figures, the total reported cost of the Army program for tuberculosis research in the 1947–1948 period was $227,752.

Navy Department

The United States Navy, through its Office of Naval Research, awarded several grants for tuberculosis research during the 1947–1948 fiscal year. According to its Bureau of Medicine and Surgery, $127,000 was appropriated for a study of the effectiveness of streptomycin on human tuberculosis in an investigation at the Naval Hospital in Corona, California. Other studies on streptomycin were already under way. Grants of $9,300 for a study of minimal tuberculosis among low-income groups, $26,700 for clinical and experimental research in thoracic surgery and pathology, and approximately $25,000 for investigations in chemotherapy and tuberculosis and silico-tuberculosis represented further studies under sponsorship of the Navy. Additional grants included $8,041 for an investigation of the biochemistry of chronic occupational disease, and $7,000 for a cooperative research project concerned with the metabolism of the tubercle bacillus using carbon$_{13}$ as a tracer element.

As outlined above, the total tuberculosis research program reported by the Navy for the 1947–1948 fiscal year represents an allocation of $203,041.

Veterans Administration

The Veterans Administration financed studies on the effect of streptomycin in tuberculosis in the amount of $1,767,000 for 1947–1948, and 24 study units were included in the investigations (7, 8, 9). A study of the incidence of tuberculosis among student veterans, recommended by the Subcommittee on Tuberculosis of the National Research Council, which acts in an advisory capacity to the Veterans Administration in the establishment of studies aimed at improved medical care for veterans, was carried out at a midwest university at a cost of $3,333.

Reported figures show a total allocation by the Veterans Administration of $1,770,333 in 1947–1948 for tuberculosis research.

Thus, according to reports received, the cost of tuberculosis research within the Federal Government in the 1947–1948 fiscal year amounted to $3,636,250. Of this figure, $3,001,200 was the reported cost of research with streptomycin and other chemotherapeutic agents.

State, County, and Municipal Health Departments

At present, data on tuberculosis research in state, county, and municipal health departments are inadequate. Perhaps the deficiency can be explained by the fact that until the program of laboratory procedures is more clearly defined through the experimental studies of the Tuberculosis Control Division of the Public Health Service, and the present shortage of trained personnel has been overcome, establishment of research projects must lag.

An experimental program of BCG vaccination, sponsored by the Pennsylvania Department of Health, was reported at an approximate cost of $10,000 for the period 1947–1948. This study is being carried out with federal funds as part of the grants-in-aid to states from the Public Health Service.

Additional research made possible by funds from official agencies included BCG studies at the University of Illinois, at a reported cost of $40,000 to the Chicago Municipal Tuberculosis Sanitarium during the 1947–1948 period, and a study of the efficacy of streptomycin in the treatment of tuberculosis reported by the University of Pittsburgh and sponsored by the Pittsburgh Department of Health through a grant of $72,000 during 1947–1948.

During 1947–1948, the New York State Department of Health, Division of Tuberculosis Control, carried out studies on the bacteriology and serology of tuberculosis, BCG production and administration, and improvement of culture media at an estimated reported expenditure of $55,800 of state funds.

This brings the total contributions for tuberculosis research reported by official agencies to $3,814,050, with $3,073,200 devoted to studies of chemotherapeutic agents.

In the period covered by the survey, much clinical research was carried out in tuberculosis sanatoriums, general hospitals with tuberculosis departments, and other institutions for the care of patients with this disease. There are more than 800 such establishments in the United States, most of which are supported by federal, state, county, or city funds. During 1947–1948 several studies, including investigations of the effectiveness of chemotherapeutic agents in tuberculosis, were financed by grants, as indicated in the allocations of official agencies already mentioned or included in the following pages showing contributions by other groups. In addition, a sizeable amount of the cost of clinical research was absorbed in the cost of medical care. The latter cannot be estimated.

Voluntary Agencies

National Tuberculosis Association and its Affiliates

Ever since the establishment of its Committee on Medical Research in 1920, the National Tuberculosis Association has continuously supported research studies in basic, background, and applied research with adaptation of research findings to experimental, demonstration, or clinical purposes (10). In proportion to its budgetary limitations, funds allocated for medical research have increased from $500 in 1920 for a study of the anatomy of the lung by the late William Snow Miller, to $95,550 in the fiscal year 1947–1948 for financing of 19 projects by qualified investigators. To the latter figure should be added approximately $10,000 for administrative costs within the Association. During the fiscal year about $40,000 was contributed by state and local tuberculosis associations for research studies recommended by the Committee on Medical Research and Therapy of the American Trudeau Society, Medical Section of the Association. In addition, some states sponsored research projects within their own borders and available figures indicate an expenditure of $66,624, which includes $28,533 for studies on chemotherapy. Of the $40,000 mentioned above, $15,000 (included in the figure of $95,550) was appropriated for research with streptomycin in the treatment of tuberculosis. The remainder was set up as a reserve fund for inauguration of new projects and establishment of a fellowship program during the fiscal year 1948–1949.

Besides streptomycin research, the studies sponsored in the 1947–1948 fiscal year by the Committee on Medical Research and Therapy fell into three broad groups: (*1*) clinical and epidemiological; (*2*) basic laboratory; and (*3*) laboratory programs of a special service type.

In his report of May 17, 1948 (11) to the National Tuberculosis Association and its affiliates, Dr. Esmond R. Long, Director of Medical Research and Therapy, described the investigations as follows:

In the first group were noteworthy investigations of the course and prognosis of tuberculosis of minimal extent, particularly as it is observed in nurses, and studies on the prognosis of tuberculosis in children and its relation to the tuberculosis of adult life. Included in these studies were fundamental investigations on the significance of the tuberculin test and the differential diagnosis of minimal tuberculosis and other pulmonary diseases causing subacute and chronic pulmonary infiltrations with a radiological appearance like that of tuberculosis. Coordinated with this group were certain investigations on the effect of pregnancy on tuberculosis, and a study of the protective value of masks against infection with large doses of tubercle bacilli.

The basic laboratory studies included investigations long under way on the chemistry of the tubercle bacillus and the relation of specific fractions of the bacillus to the pathology and immunology of tuberculosis. Another group of studies included investigations on the enzyme systems concerned with the special type of tissue necrosis characteristic of tuberculosis, viz., caseation and the phenomenon of softening of caseous tissue and cavity formation. Other studies were concerned with the physiology and pathology of the lungs. Finally, investigations on mycology, stimulated by certain similarities of tuberculosis and histoplasmosis, broadened the scope of the laboratory investigations.

The service laboratory programs included: (*1*) provision of a depot for standard strains of tubercle bacilli on which qualified investigators may draw to ensure comparability of their basic materials with those employed by other investigators; and (*2*) a group of studies designed to improve laboratory procedures in the diagnosis of tuberculosis to furnish standard techniques for inclusion in the "Diagnostic Standards" of the Association.

The budget of the National Tuberculosis Association for the fiscal year 1947–1948 also included $32,505 for statistical and social research on tuberculosis. The studies were concerned with: (*1*) continued compilation of state laws now in effect with regard to control of the disease, such as those having to do with the Means Test as a prerequisite for sanatorium care, disposition of the recalcitrant patient, case reporting methods, et cetera; (*2*) analysis of contact examinations, primarily household contacts; (*3*) further assistance in the establishment and use of central tuberculosis case registers in health departments throughout the country; (*4*) analysis of tuberculosis morbidity and mortality trends in the United States and foreign countries; (*5*) assistance to state and local tuberculosis associations in the promotion of statistical research; and (*6*) special studies as requested by various departments of the parent organization.

Allocation of funds for historical research for the fiscal year 1947–1948

amounted to $5,571 for continued assemblage of important documents and recording the history of the National Tuberculosis Association.

Thus, the total reported research program of the National Tuberculosis Association and its affiliates for the fiscal year 1947–1948 was $210,250, with $43,533 of this amount allocated to investigations with chemotherapeutic agents in tuberculosis.

Foundations

According to "American Foundations and Their Fields" (Sixth Survey (12)), there has been a rise in the number of foundations in the country from 23 in 1915 to about 600 in 1947–1948. The responsibilities and interests of these organizations are necessarily broad and varied, however, and a review indicated that probably only a small number were committed to medical research and, specifically, to research in tuberculosis.

Letters were sent to 23 foundations. Of these, three reported sponsorship of studies in tuberculosis research; 15 advised that for various reasons tuberculosis research was not included in their medical research programs for 1947–1948; and 5 did not reply.

The Commonwealth Fund reported an expenditure of $48,075 for laboratory studies on constitutional factors in tuberculosis, investigations of chemotherapeutic agents, statistical and epidemiological research, and support of two fellowships. The John and Mary R. Markle Foundation contributed $4,000 for nutritional studies in relation to tuberculosis and the Rockefeller Foundation allocated $18,532 for an epidemiological study of the disease in Williamson County, Tennessee. It is probable that other broad investigations supported by these foundations, and not covered by these figures, included some tuberculosis research.

In correspondence with universities and others, it was learned that additional contributions for this group included: $8,500 by the Lillia Babbitt Hyde Foundation; $12,000 by the Josiah Macy Foundation; $2,400 by the Lessing J. Rosenwald Foundation; and $2,500 by the Henry Oakes Foundation, the latter for studies in aluminum therapy of silicosis and the detection of early growth of tubercle bacilli.

Total support for tuberculosis research reported for 1947–1948 by this group, amounted to $96,007.

Foundations with direct research programs include the Charles Cook Hastings Home, an endowed institution with a reported annual budget of $81,550, of which $47,711 has been estimated to be for research on nutrition in tuberculosis; the Mayo Foundation and Clinic, which estimated its annual expenditure at approximately $50,000 for experimental and clinical research in tuberculosis antibacterial therapy; and the Edward L. Trudeau Foundation and the Colorado Foundation for Research in Tuberculosis, both of which are supported by funds from various sources.

The Trudeau Foundation, long established as a tuberculosis medical research center, was engaged in numerous projects in basic and applied research during

1947–1948. A large proportion of support for these investigations was derived from official and voluntary agencies, foundations, pharmaceutical houses and other industrial organizations, the cost of which is included in the appropriate group. In addition, however, funds from private and other sources, as well as interest and dividends from the Foundation's endowment, were reported at approximately $36,116.

The Colorado Foundation reported an expenditure of $13,619 for its 1947–1948 fiscal year, involving two investigations, viz., a study of antibiotics derived from Fusaria active against the tubercle bacillus, and a study of the metabolism of the tubercle bacillus. Funds for support of these projects were derived from private sources and from the endowment fund of the Foundation.

The National Jewish Hospital at Denver, a national, nonsectarian, tuberculosis medical center, with funds donated by private sources, mostly individual contributions, reported an expenditure of $46,888 for tuberculosis research in its 1947–1948 fiscal year.

Allocations for tuberculosis research during 1947–1948 as reported by the second group of foundations amounted to $194,334, and the total reported by the two groups was $290,341. Of this total, $57,906 was designated as having been specifically allocated for studies on chemotherapy in tuberculosis.

Manufacturing Firms

Commercial organizations are contributing in large measure to the program of tuberculosis research. This support is divided mainly into two groups, viz., pharmaceutical houses and firms manufacturing X-ray equipment. The former group has done much to increase knowledge of the effectiveness of chemotherapeutic agents in the treatment of tuberculosis through studies under direct supervision and grants-in-aid to responsible investigators in universities and hospitals, while the latter group has promoted research within its own laboratories for improvement of machinery for the detection of tuberculosis.

Pharmaceutical Houses

In this survey, letters were sent to 10 pharmaceutical concerns. Replies indicated that all were carrying on some research in tuberculosis. Although the majority of the studies were concerned with chemotherapeutic agents, such as streptomycin, diasone, promizole, and subtilin, also included were investigations of the use of vitamins in tuberculosis therapy, the action of certain drugs following pneumonectomy and similar surgical procedures, and employment of the adrenal cortical hormone to overcome adrenal cortical insufficiency caused by tuberculous involvement of the adrenal gland.

Eight experimental studies of the effect of streptomycin in the treatment of tuberculosis, sponsored by the American Trudeau Society (4, 5) were made possible by the contribution of more than $1,000,000 worth of the drug by six commercial firms. Results of these investigations are being published in book form by the National Tuberculosis Association. This research was supported by

the Abbott Laboratories, Eli Lilly and Company, Merck and Company, Charles Pfizer and Company, E. R. Squibb and Sons, and The Upjohn Company.

Additional research with chemotherapeutic agents in tuberculosis, as well as with other drugs already mentioned, was supported by the six organizations named above and the four remaining commercial firms to which inquiry was directed, viz., Hoffman-LaRoche, Inc., Parke, Davis and Company, Sharp and Dohme, and Wyeth Inc.

Because of their extensive and interrelated research programs, several manufacturers stated that the amount devoted exclusively to tuberculosis research was difficult to estimate and the reported figures are therefore incomplete. However, estimated contributions of the 10 pharmaceutical houses, based on replies received, amounted to $1,881,675, of which about $1,204,500 was spent for research with chemotherapeutic agents. The remainder, devoted to other studies in tuberculosis research, also included a small number of fellowships.

In reports from the foundations, it was learned that during 1947–1948 grants for chemotherapeutic research in tuberculosis were made by the Bristol Laboratories and the Eaton Laboratories amounting to $4,400. This increases the total contributions from 12 pharmaceutical houses to $1,886,075, and the amount for investigations with chemotherapeutic agents to $1,208,900.

Other Industries

Also in reports received from the foundations, it was found that other industries, principally light and heavy metal manufacturing and mining operations, contributed $83,550 during the 1947–1948 period, of which it was stated 50 per cent could be designated for research on tuberculosis and silicosis.

Firms Manufacturing X-ray Equipment

Between World War I and World War II, knowledge of the value of roentgenographic examination as a diagnostic procedure for tuberculosis was greatly increased and research was responsible for marked improvement in X-ray equipment, making possible extensive mass chest roentgenographic surveys of the civilian population. Also, screening at induction and separation centers in World War II was a routine practice in an effort to prevent induction of persons with this disease into the armed forces and to detect tuberculosis on discharge. Without continuous research on the part of the manufacturing firms, such programs could not have been undertaken.

In the present survey, letters were sent to 13 firms manufacturing X-ray equipment. Of these, 12 reported research programs and one did not reply. Reported contributions by this group, which might fairly be designated as for tuberculosis research during the 1947–1948 period, amounted to approximately $276,250. The 12 firms which reported studies carried out in their laboratories were: Ansco, George W. Borg Corporation, E. I. DuPont de Nemours and Company, Eastman Kodak Company, Fairchild Camera and Instrument Corporation, General Electric X-ray Corporation, Kelly-Koett Manufacturing Com-

pany, Machlett Laboratories, North American Philips Company, Powers X-ray Service, Standard X-ray Company, and Westinghouse Electric Corporation.

Universities

In considering the part played by the universities, it is necessary to state at the outset that this survey includes only the 70 medical schools designated at the time as approved by the American Medical Association (13). It is fair to assume that some research in tuberculosis is being carried out in other institutions and in the smaller colleges. Although it is not feasible to include research expenditures of such schools in this report, it is obvious that schools of public health, schools of public health nursing, and sociology departments of various colleges make expenditures for research bearing directly or indirectly on tuberculosis. It may be noted also that the American College Health Association, through its Committee on Tuberculosis, carries out an annual survey, in cooperation with the National Tuberculosis Association, of the extent of tuberculosis among college students. This might justifiably be termed tuberculosis research.

Replies to the 70 letters mailed to schools of medicine indicated tuberculosis research projects in 39. Of the remaining 31, 20 reported studies in prospect or expressed an interest, and 11 simply indicated that no tuberculosis research was carried out during the time specified in the inquiry.

In the period 1947–1948, grants to the 39 universities or institutions incorporated or affiliated with them, such as the Henry Phipps Institute in Philadelphia, amounted to approximately $500,000. This support was derived from official and voluntary agencies, foundations, and manufacturing firms, and the sums have already been included appropriately in the foregoing pages. However, the universities *per se* make a substantial contribution of personnel, laboratory facilities, supplies, et cetera, to augment the grants-in-aid of research received from outside sources. According to reported figures, an approximation of funds furnished by the universities during 1947–1948 was $134,400. In addition, funds from private sources, mostly individuals, donated directly to the universities and allocated for tuberculosis research during the same period, were reported to be approximately $57,000.

Thus, the total contribution of the 39 universities for tuberculosis research in 1947–1948 was $191,400. This figure seems low, and represents only reported sums. Because the same laboratories may be used for research in other fields and personnel may be interested in several research projects, it is difficult to arrive at a true estimate; the total expenditure of the universities was probably much higher than is shown here.

COMMENT

As has been indicated, support for tuberculosis research in the United States comes from the official agencies (mainly the federal group), voluntary agencies, foundations, manufacturing firms, and universities. The contributions of the five groups as calculated from their reports for a twelve-months' period during 1947–1948, and the proportion devoted to studies in chemotherapy of tuberculosis, are shown in table 1 and figures 1 and 2.

Reflected in the following figures is the interest in the last few years in streptomycin and other chemotherapeutic agents which have shown promise in the treatment of tuberculosis. The reported allocation for investigations in chemo-

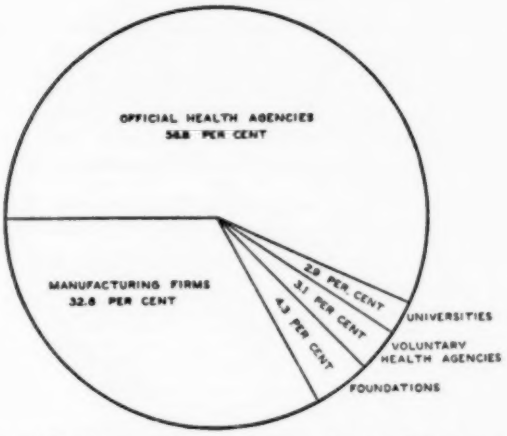

FIG. 1. Total contributions to tuberculosis research, classified by contributing agency, 1947–1948.

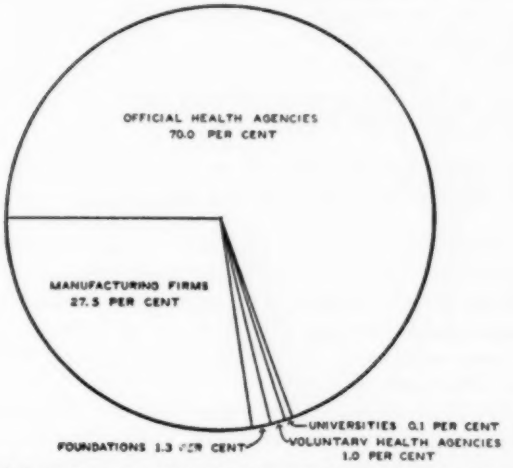

FIG. 2. Cost of chemotherapy studies in tuberculosis, classified by contributing agency, 1947–1948.

therapy of tuberculosis represents approximately two-thirds of the cost of the total tuberculosis research program in this country during a twelve-months' period in 1947–1948.

Primarily, according to the survey, official agencies supported background, applied, and developmental research in tuberculosis. The National Tuberculosis Association, the voluntary agency, was engaged to a large extent in basic and developmental research, and a few projects of the same type were reportedly supported at the state and local level.

The foundations which furnished grants-in-aid sponsored studies in all four categories of research, governed, no doubt, by the types of requests received which seemed to indicate proposals promising addition to the knowledge of tuberculosis or furthering its control. The second group of foundations, *i.e.*, those with direct research programs, were engaged largely in basic research studies, although background, applied, and developmental research projects formed a part of their work.

TABLE 1

Total Allocations for Tuberculosis Research and Cost of Chemotherapy Studies in Tuberculosis, Classified by Contributing Agency, 1947–1948

Calculated for a twelve-months' period

CONTRIBUTING AGENCY	TOTAL CONTRIBUTIONS TO TUBERCULOSIS RESEARCH	COST OF CHEMOTHERAPY STUDIES IN TUBERCULOSIS
All agencies	$6,710,141.00	$4,388,039.00
Official health agencies	3,814,050.00	3,073,200.00
Manufacturing firms	2,204,100.00	1,208,900.00
Foundations	290,341.00	57,906.00
Voluntary health agencies	210,250.00	43,533.00
Universities	191,400.00	4,500.00*

* Except for intangibles, chemotherapy studies in tuberculosis in universities are, in general, supported by grants from other agencies listed in the table.

The program of the manufacturing firms was concerned particularly with applied and developmental research but included also investigations in basic research.

The greatest contribution of the universities was their reservoir of personnel and laboratory facilities, the cost of which cannot be accurately reckoned. Potential expansion of basic research by inauguration of additional studies by qualified investigators, and through a program of graduate and undergraduate fellowships for promising young research workers, rests largely with this group in respect to personnel and facilities.

In conclusion, it must be stated that large sums were spent by official and voluntary agencies for tuberculosis case finding through mass chest roentgenographic surveys and health education of the public during the period covered by this report. In addition, much clinical research in tuberculosis was absorbed in the costs of medical care, to which individuals and many community health and welfare organizations contributed (14, 15). Although the importance of this phase of the program is well recognized, the amount of funds which could be designated for tuberculosis research is impossible to estimate.

Acknowledgment

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THE RESECTED POSTTHORACOPLASTY LUNG[1, 2, 3]

A Clinico-pathologic Correlation

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INTRODUCTION

In the past two decades, thoracoplasty has become one of the safest and most effective measures for the treatment of pulmonary tuberculosis. During this time, the technique of performing the operation has improved. Moreover, increased experience has resulted in a better selection of patients on whom the procedure has been performed so that good clinical results are obtained in the majority of instances. Unfortunately, however, there is a sizeable percentage of patients receiving this treatment who continue to have either sputum positive for tubercle bacilli, persistence of cavity, or both. This group of patients constitutes the "thoracoplasty failure" as considered in this study.

The reasons for thoracoplasty failure are obviously of interest and of considerable importance. At times, one can surmise from the clinical evaluation why the treatment failed. In other cases, the autopsy findings may assist in answering the question (1). Neither of these approaches is entirely satisfactory, however, because they do not allow a clinico-pathologic correlation at the proper time. The autopsy findings in a patient dead from pulmonary tuberculosis are not the same as those in a living patient prior to the terminal phases of the disease.

Thoracoplasty failure can be treated by revision thoracoplasty, cavernostomy, or by pulmonary resection. In recent years, pulmonary resection has been used with increasing frequency and the lungs thus removed have allowed, for the first time, the opportunity to study the pathology of the disease in the living patient. It is hoped that the present clinico-pathologic study may further the understanding of the basic reasons for thoracoplasty failure and permit more rational selection of patients for thoracoplasty and resection.

MATERIAL AND METHODS

During the years 1934–1948, inclusive, 323 pulmonary resections were performed for tuberculosis by the Overholt Thoracic Clinic. Thoracoplasty failure was the indication for resection in 64 instances. Since 2 of the 64 cases had various complications prior to the thoracoplasty (empyema, fistula, and previous

[1]From the Laboratory of Pathology, New England Deaconess Hospital and the Overholt Thoracic Clinic, Boston, Massachusetts.

[2]Presented before the Medical Section, as part of the symposium on *Surgery*, at the 45th annual meeting of the National Tuberculosis Association, Detroit, Michigan, May 5, 1949.

[3]The pathologic studies were made possible through a grant from the Committee on Medical Research and Therapy of the American Trudeau Society, Medical Section of the National Tuberculosis Association.

lobectomy), they were not included in the present study, which is based on a clinical and pathological evaluation of the remaining 62 cases.

The pathological findings in each case have been reviewed and have included microscopic examination of multiple areas of the parenchyma as well as of the individual segmental and larger bronchi. Of prime interest in the pathologic review were: (*1*) tabulation of important sites and types of active tuberculosis; (*2*) search for possible anatomic causes to explain the pathogenesis of the failure of collapse therapy. In only 4 instances was the pathological material not available for satisfactory review.

The clinical course of the 62 cases was likewise reviewed. Although follow-up observations were available for all of the cases, an adequate review of preresection roentgenograms was not possible in 8 instances. In the remaining 54 cases, the roentgenograms and clinical courses were reviewed with particular reference to type of disease and to apparent clinical causes of thoracoplasty failure.

Table 1 gives the general statistics for this group of patients and is self-explanatory. However, certain facts bear emphasis. There is one more resection than the number of patients because one patient had two lobectomies (pneumonectomy in 2 stages).[4] It should be noted that pneumonectomy was performed in 45 of the 62 patients because the distribution of disease in the thoracoplasty-failure group does not usually lend itself well to lobectomy. Only three segmental resections were performed in combination with lobectomy and these were done in preference to pneumonectomy only because of the poor reserve of the patient or very questionable contralateral disease.

The age of patients varied from 19 to 49 years. Over 50 per cent (33) were between 30 and 40 years. It is interesting that none was over 49 years of age, although a significant number of the entire resection series are above this age. There was a predominance of females, as is true with most series of resections.

The duration of illness varied from fifteen months to thirty years. Only 48 per cent had been ill for less than two years; 37 per cent had been ill for two to five years; 40 per cent from five to ten years; and 18 per cent over ten years. Thus, resection in this group represents surgical treatment predominantly in middle-aged patients with long-term illnesses. It is not surprising, then, that 44 of the 62 represent failures, not only of thoracoplasty, but of a combination of collapse therapy measures as listed in table 1. Only 18 patients had no prethoracoplasty collapse therapy. In addition, 14 had revision thoracoplasty, 4 cavernostomy, and pneumonectomy had been attempted elsewhere on one patient. There were 36 patients who had contralateral lesions which were considered either controlled or controllable in each instance.

Bronchoscopy was not performed in 7 patients. Of the remainder, 30 had negative findings on bronchoscopic examination and endobronchial tuberculosis was present in 23. Attention is called to the fact that 15 of these lesions were

[4]Right upper and middle lobectomy was first performed on this patient. Her sputum remained positive and the lower lobe was removed at the second operation. The cause of failure on pathological examination was ulceration of the middle lobe stump.

TABLE 1

General Statistics

Clinical and Pathological Evaluation of 62 Cases of Thoracoplasty Failure

Total Number of Patients			62
Males			21
Females			41
Operations Performed			63
Pneumonectomies			46
Right			21
Left			25
Lobectomies			17
R.U.L.			5
R.U. and M.			3
R.U. and Sup. Div. Rt. L.L.			1
R.U. and M. and Sup. Div. R.L.L.			1
L.U.L.			6
L.U. and Sup. Div. L.L.L.			1
Duration of Disease (15 months to 30 years)			
1 to 2 years	3	(4.8 per cent)	42 per cent
2 to 3 years	7		
3 to 4 years	11		
4 to 5 years	5		
5 to 10 years	25		40 per cent
10 to 15 years	6		18 per cent
15 to 20 years	4		
20 to 25 years	0		
30 years	1		
Previous Therapy			
A. Ipsolateral Lung			
Pneumothorax			24
Phrenic			22
Pneumoperitoneum			3
Cavernostomy			4
Attempted pneumonectomy			1
Revision thoracoplasties			14
B. Contralateral Lung			
Pneumothorax			6
Contralateral Disease (36 of 62 Patients)			
23 of 45 pneumonectomies			
13 of 17 lobectomies			
Endobronchial Disease			
Negative bronchoscopy			32
No bronchoscopy			7
Positive bronchoscopy			23
a. submucosal	6		
b. ulcerative	2		
c. ulcerostenosis	6		
d. fibrostenosis	9		

obstructive in type, 6 being ulcerostenosis and 9 fibrostenosis. Distribution of these obstructing bronchial lesions is similar to that reported in 1945 (2), with 47 per cent in the left main bronchus and 73 per cent of the total in the left main bronchus or right upper lobe orifice. No stenotic lesions were seen below the level of the superior division of the lower lobe. Only two lesions involved the trachea and these were extensions from the right main bronchus.

PATHOLOGY

In evaluating the pathology of the resected lung, the first consideration was given to a determination of the types and sites of active tuberculosis which were capable of producing sputum positive for tubercle bacilli. From such an analysis, the types of pathology readily fell under three headings (table 2): (a) active tuberculous cavity; (b) endobronchial tuberculosis; (c) extensive parenchymal tuberculosis. Many specimens had more than one type or site of major pathology, which accounts for a total greater than the number of specimens.

TABLE 2

Types of Tuberculous Disease

Active tuberculous cavity		50
Multiple	5	
Lower lobe	9	
Endobronchial tuberculosis		40
Stenosis	7	
Bronchiectasis	10	
Extensive parenchymal tuberculosis		9

In many instances, there were scarred foci encountered which unquestionably represented healing or healed cavities, but these were not tabulated. In one specimen, an epithelial-lined cavity showing no evidence of active tuberculosis was found. This, likewise, was not included in the tabulation. There were 50 specimens which showed cavities and multiple cavities were present in 5 instances. While the commonest site for cavity was the apical posterior segment of the upper lobe, they were found elsewhere as well. The average size of the upper lobe cavities was 2 to 3 cm. in greatest diameter. The nine lower lobe cavities were notably larger, however, and, as a group, averaged several times the size of those found elsewhere.

Endobronchial tuberculosis was of three types: (a) stenosis (either hyperplastic or fibrous); (b) tuberculous bronchiectasis; (c) diffuse mucosal and submucosal disease (table 2). The endobronchial disease tabulated was arbitrarily limited to that involving segmental or larger bronchi and was proved to be tuberculous by microscopic examination. While diffuse tuberculosis of the mucosa and submucosa of one or more segmental bronchi was usually the only bronchial finding, in 10 cases there was an associated tuberculous bronchiectasis and in 7 specimens there was stenosis of the orifice of a large bronchus. The distri-

bution of the bronchial disease will be reported in a future study. It will be noted that the incidence of stenosis was not as high in the pathological specimen as was the incidence as determined by bronchoscopy. This is because the lung was at times resected through, or just distal to the stenotic area. A cavity was usually, but not always, present when there was endobronchial disease of any type. If a cavity was present, the disease of the bronchi was not necessarily limited to the segment or lobe containing the cavity.

Extensive parenchymal disease was a prominent pathologic feature in 9 specimens but was always associated with either cavity, endobronchial disease, or both.

The second item of pathologic interest was a determination of possible pathogenetic factors in the thoracoplasty failure. Items included under this heading were: (a) thick, fibrous cavity wall; (b) thick, fibrous, or calcified pleura; (c) lower lobe cavity; and (d) severe endobronchial disease of the stenotic or bronchiectatic type (table 3).

The presence of a very thick, fibrous wall around a cavity obviously acts as a deterrent to the proper collapse which should be expected from thoracoplasty; such a factor was found in 5 specimens. Similarly, a markedly thickened or calcified pleura resists adequate collapse, and was considered to be an anatomic feature predisposing to failure in 7 instances. Fibrosis of the parenchyma itself was undoubtedly a factor in failure frequently but, since it was so difficult to evaluate from the examination of the pathology alone, it was not tabulated.

Extensive disease, with or without cavitation, is not listed as an anatomic reason since it may equally well represent a manifestation of failure. There is one exception to this, however. Cavities in the lower lobe (9 cases) were notably large and poorly collapsed as compared to those elsewhere in the lung. Such a finding was constant enough to warrant listing the location of a cavity in the lower lobe as a pathogenetic reason for thoracoplasty failure.

Endobronchial disease of the stenotic or bronchiectatic type was present in 17 specimens and in each was considered anatomically to be a predisposing factor to failure (figures 1, 2). This is particularly true when the endobronchial tuberculosis has become severe enough to be independent of its parent parenchymal focus (3).

In addition to the causes listed, there were many other conditions which may have played an anatomic, basic role in the pathogenesis of the thoracoplasty failure. It was apparent, however, that the complete evaluation and explanation of the causes of thoracoplasty failure cannot be made from the pathological specimen alone. In the majority of instances, a clinico-pathologic correlation is necessary.

CLINICAL CAUSES FOR THORACOPLASTY FAILURE

Table 4 records the clinical factors contributing to thoracoplasty failure in the 54 patients upon whom complete data, including prethoracoplasty and preresection roentgenograms, were available. The factors listed here are those commonly found in the literature (4). However, the term "tension cavity" has been

TABLE 3

Factors in Pathogenesis of Failure

Thick cavity wall	5
Thick pleura	7
Lower lobe cavity	9
Endobronchial disease	17
Stenosis or bronchiectasis.	

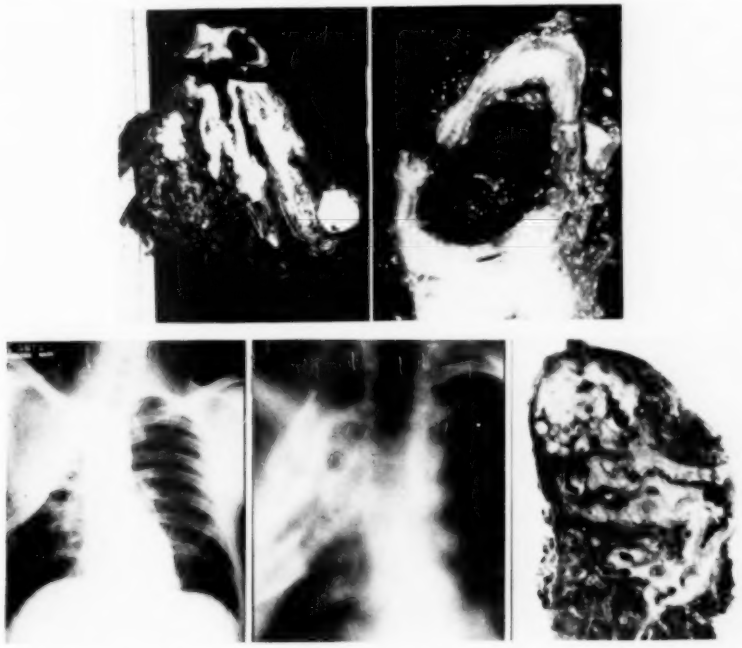

FIG. 1. Bronchial disease and tuberculous bronchiectasis: Mr. F. H., age 49. (Upper left) Duation of disease 4 years prior to thoracoplasty and 12 years prior to resection; hyperplartic endobronchial stenosis of lobar bronchus with extensive bronchial involvement distalsy. (Upper right) Enlargement of stenotic bronchus.

FIG. 2. Good thoracoplasty—residual cavity and extensive bronchial disease: Mr. W. G., age 27. Duration of disease 8 months prior to thoracoplasty and 20 months prior to resection. No endobronchial disease present bronchoscopically. (Lower left) A postthoracoplasty roentgenogram demonstrates adequate collapse; (Center) Laminogram reveals presence of cavity in collapsed area; (Lower right) Surgical specimen contains an upper lobe cavity (2.3 cm.) and much endobronchial disease.

intentionally avoided because of the difficulty in determining just when a cavity falls into this category.

Inadequate surgery was an outstanding feature in this group of patients (figure 3). Adequate collapse of the cavity-bearing area was obtained in only

14 instances. Totally inadequate collapse was present in 40 cases. The factors causing this failure of collapse are listed and are self-explanatory except that delayed stages were probably a more common cause than is indicated. One patient had a flaccid chest wall as the result of an extensive apicolysis with failure of regeneration of ribs. Naturally, resection was the only therapy that could be offered this patient for her residual disease.

The size, number, and location of cavities were undoubtedly contributory causes of failure in many of these patients. These factors, singly or in combination, were present in 36 cases. Predominantly exudative disease was present in 11 cases at the time of thoracoplasty. Spread of the disease to the base of the lung occurred in 4 and became one of the major causes of failure in these patients

TABLE 4

Clinical Causes for Thoracoplasty Failure
(54 patients)

A. *Inadequate Surgery*	40
1. Transverse processes not resected	25
2. Long anterior stumps	11
3. Inadequate number of ribs resected	16
4. Delayed stages	4
5. Failure of rib regeneration	1
B. *Factors Related to Tuberculous Disease*	
1. Characteristics of cavity	
a. Large cavity (4 to 6 cm.)	26
b. Giant cavity (6 cm.+)	9
c. Multiple cavities	13
d. Unfavorable location	8
2. Exudative disease	11
3. Spread of disease to base	4
4. Endobronchial tuberculosis	21
C. *Mechanical Factors*	
1. Thickened pleura	9
2. Presence of pneumothorax	8
3. Bronchiectasis	3
D. *No Evident Clinical Cause of Failure*	4

(figure 4). Endobronchial disease was present in 21. It was submucosal in type in 6, ulcerative in 2, ulcerostenotic in 6, and fibrostenotic in 7.

The pleura was sufficiently thick in 9 cases to interfere with relaxation of the chest wall. Pneumothorax was present in 8 and displaced the cavity inferiorly and medially in each case. Bronchiectasis was clinically evident in 3.

In 4 patients no clinical cause of failure could be determined.

COMMENT

One factor that hampered the adequate analysis of the material was the difficulty in distinguishing pathologically between cause and effect of thoracoplasty failure. Since by definition a thoracoplasty failure is a case with sputum per-

sistently positive for tubercle bacilli, any active tuberculosis which might give rise to this state is, in this sense, the pathological cause of thoracoplasty failure. From examination of the pathological specimen alone, however, it is usually impossible to be sure whether any individual type of disease or lesion is the pathogenetic cause or merely the manifestation of failure.

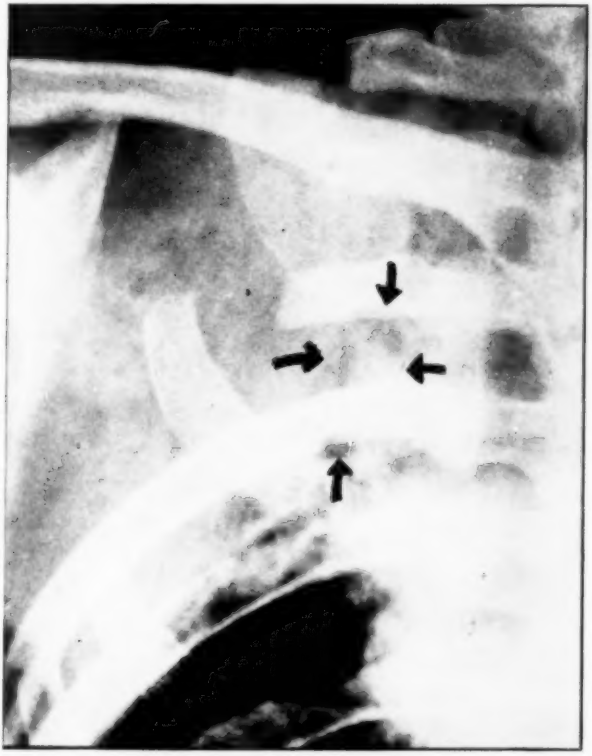

FIG. 3. Roentgenogram showing inadequate collapse: Mrs. A. D., age 46. Duration of disease 21 years prior to thoracoplasty and 30 years prior to resection. No endobronchial disease present. Roentgenogram demonstrates a poor thoracoplasty with resection of an inadequate number of ribs, presence of long anterior stumps, and posterior rib stumps with transverse processes. The cavity extends below the level of the highest unresected rib.

An additional point which made analysis and correlation more difficult was the fact that 40 of the entire group had an inadequate thoracoplasty from the surgical point of view. It is obviously unsatisfactory to study the pathology of thoracoplasty failure in a specimen if an adequate thoracoplasty has never been done.

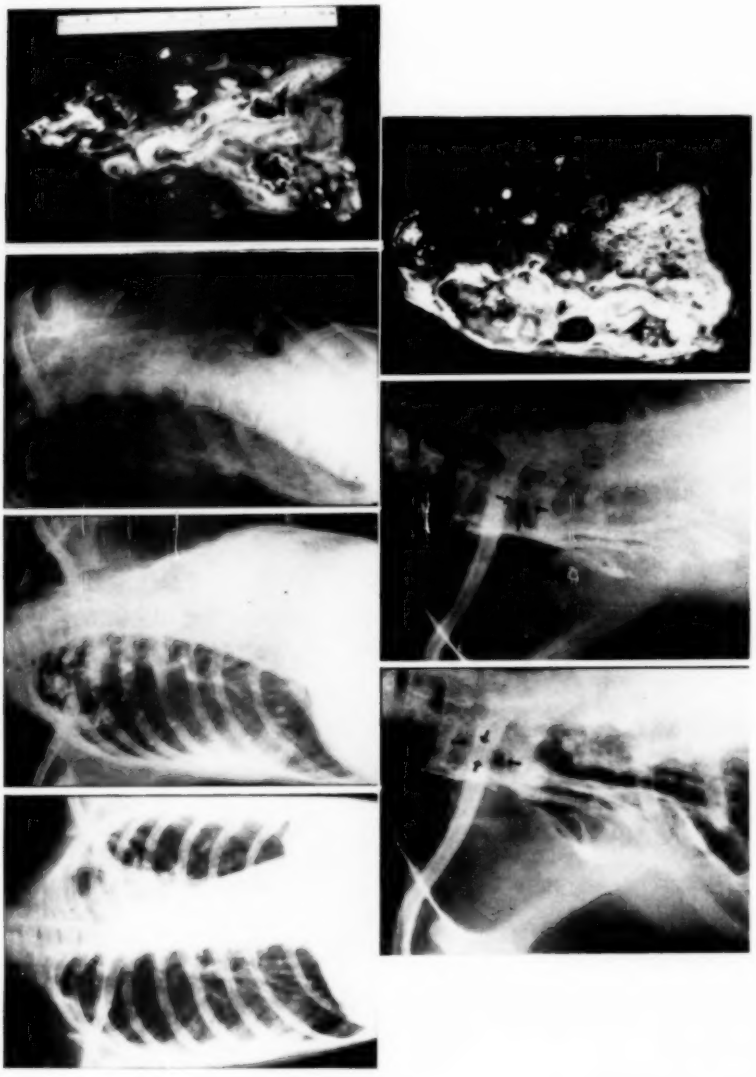

FIG. 4 (Top)
FIG. 5 (Bottom)

The 14 cases who had a thoracoplasty which was considered technically and clinically adequate made up an interesting group. Only 4 of the group had initial cavities less than 4 cm. in diameter. A review of postthoracoplasty roentgenograms and of the resected specimen revealed residual cavitation and inadequate cavity compression. These findings confirmed the impression that large and giant cavities, by their size alone, may predispose to failure of thoracoplasty even if it is adequately performed. Eleven of the 14 cases had exudative disease prior to thoracoplasty, often associated with a large cavity, some of which showed spread of disease and new cavity formation after thoracoplasty. Endobronchial disease was present by bronchoscopy in 5 cases prior to thoracoplasty. In the resected specimen, endobronchial disease was a prominent feature in 8. In 3 of the cases, no pathologic explanation for persistence of "positive" sputum was found, only a few small foci of submucosal tuberculosis being present in 2 and only extensive nontuberculous fibrosis and bronchiectasis in the third. In the final analysis of the 14 cases with adequate thoracoplasty, the features which stand out as the most probable causes of failure are large and giant cavities and exudative and endobronchial lesions, either of which may predispose to postoperative spread of disease.

In only 4 instances did the review of the charts and pre- and post-operative roentgenograms fail to show any cause for failure. These patients had satisfactory thoracoplasties with adequate collapse. Their cavities were under 4 cm. and the type of disease should have usually responded to the treatment. None of them had endobronchial disease. Cavity was found in pathological examination in 2, one a residual cavity and the other a cavity that had developed in the inferior part of the left upper lobe as a result of an undetected spread of disease. In the other 2 instances, examination of the resected specimen revealed only a small amount of submucosal bronchial disease which was not considered to be an adequate explanation for the persistent discharge of tubercle bacilli in the sputum.

DISCUSSION

The 62 patients studied were from many parts of the country and their thoracoplasties represent the work of many surgeons, including our own group.

FIG. 4. Failure because of spread of disease to base of lung: Mrs. D. P., age 38. Duration of disease 5 years prior to thoracoplasty and 18 years prior to resection. No endobronchial disease present bronchoscopically. (Upper left) Prethoracoplasty roentgenograms. Two large cavities (4.5 by 3 cm. and 4 by 3 cm.) in left upper lung field with a clear, left base (Upper left middle) Spread to base following thoracoplasty. (Upper right middle) Oblique film demonstrates new cavity formation in area of "spread". (Upper right) Resected lung reveals the upper lobe disease controlled. Two cavities in lower lobe, and gross endobronchial tuberculosis of lower lobe bronchi.

FIG. 5. Roentgenogram showing initial inadequate collapse, probably cause of later extension: Mrs. G. S., age 38. Duration of disease 9 years prior to thoracoplasty and 18 years prior to resection. A fibrostenosis of right main bronchus was present. (Lower left) Roentgenogram demonstrates inadequate thoracoplasty with long anterior stumps and cavity behind unresected transverse process. (Lower middle) The cavity persists after thoracoplasty has been revised when additional ribs resected but transverse processes left untouched. (Lower right) Surgical specimen presents a huge cavity, 10.5 by 3 cm. crossing the fissure line and bronchiectasis of the lower lobe.

Thus, they can be considered to reflect average concepts concerning case selection and what constitutes an adequate thoracoplasty. In this group, there can be no doubt that poor collapse as a result of a technically poor thoracoplasty was the outstanding cause of failure. Only the most complete thoracoplasty could possibly have controlled the majority of the lesions represented, but, in spite of this, transverse processes were not resected, long anterior stumps were left, and insufficient ribs resected in 40 of the 54 patients on whom adequate roentgenograms were available for study. In addition, in the 11 patients with obstructing lesions in the main bronchus, a complete thoracoplasty as recommended by

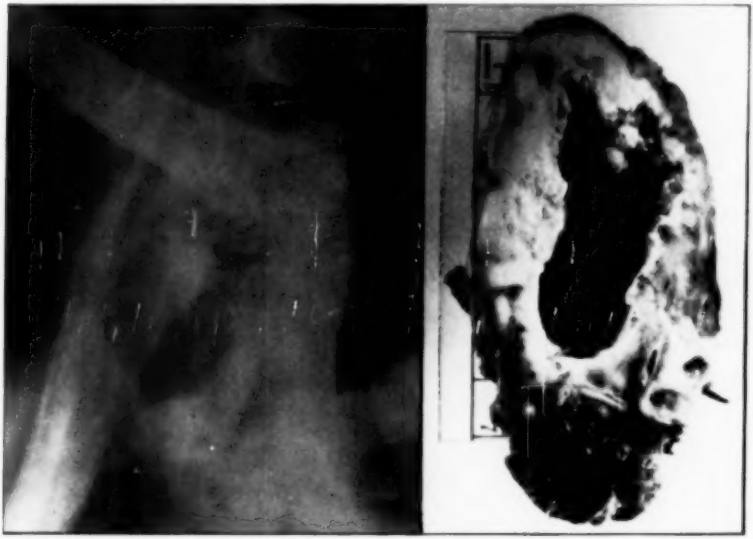

FIG. 6. Good thoracoplasty with persisting cavity, large, thick-walled cavity with extensive caseation: Miss D. G., age 34. Duration of disease, 2½ years prior to thoracoplasty and 4 years prior to resection. There was no endobronchial disease or bronchoscopy. (Left) Roentgenogram demonstrates persistence of cavity under a good technical thoracoplasty. (Right) Surgical specimen reveals a 4.0 cm. cavity with thick walls and markedly thickened pleura.

Alexander (5) was not performed in a single case. A review of the roentgenograms revealed that a poor thoracoplasty was often the initiating factor of a long series of events that eventually led to the necessity of resection (figure 5).

An analysis of this group shows that they are patients predominantly of middle age with long-term illnesses. It is not surprising, therefore, that 44 of the total 62 represent failures, not only of thoracoplasty, but of a combination of collapse therapy measures as listed in table 1. Only 18 patients had no prethoracoplasty collapse therapy. The facts indicate that this group of patients was brought to pulmonary resection late and at a time when many of them were poor risks. It is our opinion that many cases in this series represented poor case selection

for thoracoplasty and today could be treated more successfully by resection.

The third notable contributory cause to failure of thoracoplasty was a consequence of individual characteristics of the disease process (figure 6). Such characteristics include large and giant cavities which were so notable in the group with adequate thoracoplasty. An unfavorable position of the cavity in the lower lobe is another characteristic of apparent importance in that it cannot be properly compressed by thoracoplasty. Endobronchial tuberculosis, particularly when stenotic or bronchiectatic, as well as exudative disease, are likewise individual features of the disease process which seem to inhibit good results from thoracoplasty.

The fourth group of factors of importance are those of a mechanical nature which prevent adequate collapse and compression. Such features as thickened cavity wall, thick pleura, and the fibrotic indurated lung are examples of this group.

SUMMARY AND CONCLUSION

1. A clinico-pathological study of 62 instances of thoracoplasty failure in which pulmonary resection was performed is reported.

2. It is difficult, from the pathologic specimen alone, to distinguish between cause for failure and manifestation of failure. The best determination of cause can be made when the clinical findings are correlated with the pathology.

3. The outstanding contributory cause of failure was a technically inadequate thoracoplasty.

4. Poor case selection was a frequent contributory cause for failure.

5. Another reason for failure was a consequence of the individual characteristics of the disease process, such as bronchial involvement, exudative disease, large cavities, and distribution of disease.

6. Factors interfering with success of thoracoplasty also included features such as thick cavity wall, thick pleura, and a fibrotic, indurated lung, all of which interfere with collapse.

Sumario y Conclusiones

El Pulmón Postoracoplástico Resecado. Correlación Clínico-Patológica

1. Este estudio clínico-patológico comprende 62 casos de fracasos de la toracoplastia en los que se ejecutó una resección pulmonar.

2. A base exclusiva del ejemplar patológico, resulta difícil distinguir la causa, de la manifestación, del fracaso. La mejor determinación de la causa es posible cuando se correlacionan los hallazgos clínicos con la patología.

3. La más notable causa contribuyente del fracaso consistió en la insuficiencia técnica de la toracoplastia.

4. Una frecuente causa contribuyente al fracaso consistió en la mala selección de casos.

5. Otra causa del fracaso procedió de las características individuales del proceso patológico, es decir, invasión bronquial, forma exudativa de la enfermedad, tamaño de las cavernas y distribución de la dolencia.

6. El último grupo de factores que impiden el éxito de la toracoplastia com-

prende puntos tales como espesor de las paredes de la caverna, espesamiento pleural, y fibrosis e induración del pulmón, todo lo cual obstaculiza el colapso.

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Discussion of Paper by Doctor Meissner and His Associates

Dr. Donald L. Paulson, Dallas, Texas: In the surgical treatment of pulmonary tuberculosis we have a variety of procedures available to us today. Theoretically there should be no competition among these procedures. Each should be used in its proper place depending on the type of disease present and the condition of the patient, particularly from the standpoint of the patient's respiratory reserve. However, in practice it is not always possible to fit the appropriate procedure to the patient's individual needs. After a complete evaluation of his individual type of disease, various surgeons will employ a variety of procedures for the same type of disease. It is for this reason that studies such as Doctor Meissner and his associates have reported are of great value. One may not agree with the corrective procedures employed, but the reasons for failure are facts which we can accept. Perhaps these facts will bring us to more complete agreement on the type of procedure which is appropriate in a given case.

To illustrate this point, there can be no question that severe bronchial stenosis or bronchiectasis is better treated by resection. On the other hand, in the absence of bronchial obstruction and severe bronchiectasis, and in the presence of a technically inadequate thoracoplasty (40 of 54 patients), particularly in the presence of contralateral disease (36 of 62 patients), I am sure that some of us would consider a revision thoracoplasty as the more appropriate procedure over resection. This may not be true in the presence of a large cavity considered uncollapsible. But even in this instance there are safer procedures available to us such as cavernostomy, the use of extrapleural plumbage, either by pack as used by Doctor Kinsella or lucite balls as suggested by Doctor Brewer.

Thoracoplasty for various reasons if properly performed is one of the safest and most effective measures which we have for the surgical treatment of tuberculosis. In cases in which there is an honest difference of opinion between the use of thoracoplasty or resection (excluding the bronchial strictures and bronchiectasis), we believe that the thoracoplasty should be done first. If an adequate thoracoplasty is effective, one has utilized a safer procedure. If it is not effective, one can then proceed to a resection on a more justifiable basis and, I believe, with less danger of contralateral reactivation of disease and a better functional result.

Doctor Wilson and I have discussed the necessity for more studies of this type. We are in agreement that these figures and the results should be broken down according to the indication for the surgical procedure. Although I realize that this fact was not rightfully included in this paper, I believe it is pertinent to the subject as a whole to know what the results of resection were in this group of patients reported here today.

TUMORS OF THE MEDIASTINUM[1]

A Discussion of Diagnostic Procedure and Surgical Treatment Based on Experience with Forty-four Operated Cases

LYMAN A. BREWER, III, AND FRANK S. DOLLEY

(Received for publication May 5, 1949)

INTRODUCTION

Primary tumors of the mediastinum have ceased to be medical curiosities discovered principally at the autopsy table. They are now being diagnosed in increasing numbers by clinical examination. This is a result of greater interest in thoracic diseases in general, the routine employment of the chest roentgenogram as a part of the chest examination, and the use of mass roentgenographic surveys for the detection of pulmonary tuberculosis. Thus, the problem of what plan of action should be taken on the discovery of a possible mediastinal tumor is becoming more important to all physicians treating thoracic diseases. Should these lesions be disregarded because of the paucity of symptoms or is operation indicated in every case? Actually the writers believe there is a definite series of investigative procedures which, if carried out in each case, will determine in most instances whether or not a mediastinal tumor is present. This presentation is concerned with a review of these various diagnostic procedures and the therapy employed in the management of a large series of mediastinal tumors, 44 of which were treated by operation.

INCIDENCE

It is impossible to estimate the true incidence of mediastinal tumors, due to the fact that they are often diagnosed as other conditions. Primary neoplasms of the mediastinum are rare and the series reported have not been large. Heuer (1) in presenting seven years experience with tumors of the mediastinum at the New York Hospital recorded operations on 39 primary benign tumors, 17 malignant ones. In addition, 47 were classified as primary malignant tumors of the lymph nodes of the Hodgkin's lymphosarcoma group. Bradford, *et al.* (2) reported 35 cysts and tumors of the mediastinum in 1946. Blades (3) presented the combined experience of the Army Thoracic Surgery Centers in the United States during World War II. He collected 94 benign tumors and 15 malignant ones which had been subjected to surgery; 94 of the 109 cases were detected by routine roentgen examination of the chest. Our operative experience consists of 44 primary tumors of the mediastinum of which 35 were benign and 9 malignant. We have treated a greater number of malignant tumors of the mediastinum which were not considered candidates for surgery.

Little attention has been paid to the occurrence of mediastinal tumors in mass

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radiographic surveys of the chest. Prows (4) reviewed 2,821 twenty-one millimeter chest films taken as a mass survey on routine admission at a private hospital, the California Lutheran Hospital in Los Angeles, California. The results are seen in table 1. It is of interest that the incidence of suspected mediastinal tumors was equal to that of suspected pulmonary tuberculosis; 2.26 per cent of positive findings, or 0.1 per cent of the entire survey. This does not represent a true incidence of primary mediastinal tumor as many of these patients had screening chest roentgenograms or fluoroscopy before being admitted to the hospital. It does point out, however, that more attention should be paid to the mediastinum in routine roentgenographic surveys of the chest.

ANATOMY OF THE MEDIASTINUM

Figures 1 and 2 illustrate the anatomy of the right and left aspects of the mediastinum. Pressure on the various structures depicted in the drawings accounts for the various symptoms, signs, and abnormal findings of the specialized diagnostic procedures discussed later on in this presentation.

TABLE 1

Mass Chest Roentgenographic Survey of Routine Admissions California Lutheran Hospital (Prows)

Cases examined roentgenographically	2,821
Cases with positive findings, all types	177
Cases with probable pulmonary tuberculosis	5
Cases with probable mediastinal tumors	5

SYMPTOMS AND SIGNS

For a considerable period of time in the growth of a mediastinal tumor no symptoms may be produced. It is only when a "sensitive" structure in the mediastinum is pressed upon that these tumors make themselves known to the patient. Thus, a mediastinal tumor may cause considerable compression of the lung away from the hilum without causing discomfort, provided a branch bronchus is not occluded. It is not surprising that mediastinal tumors may sometimes grow to a considerable size without causing much difficulty to the patient. Once this fact is well understood the clinician will not be surprised to have the presence of these tumors discovered by a routine or survey chest roentgenogram.

The symptoms produced by a mediastinal tumor may be classified according to the disturbance in function of the various organs in the mediastinum. The severity of symptoms depends upon the size and location of the tumor, the rapidity of growth, and the presence or absence of actual invasion of those organs. Five main groups of symptoms may be recognized: (*1*) neurological, (*2*) respiratory, (*3*) gastro-intestinal, (*4*) vascular, and (*5*) miscellaneous.

Neurological: Probably one of the earliest and most constant symptoms of tumors of the mediastinum is the feeling of a vague intrathoracic discomfort, fullness, or ache. This is common in the tumors that press on portions of the

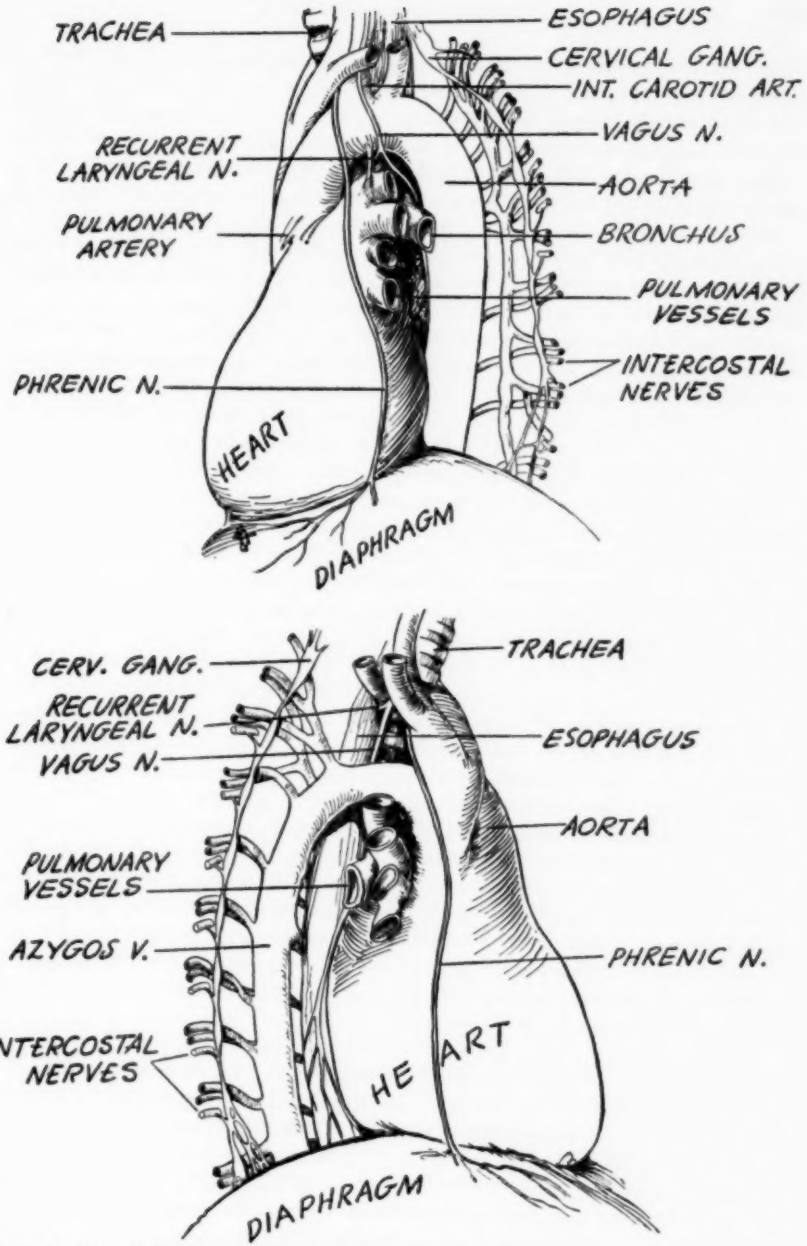


FIG. 1. (Upper) Drawing of anatomy of left view of mediastinum.
FIG. 2. (Lower) Drawing of anatomy of right view of mediastinum.

chest wall and so affect the sensitive intercostal nerves. Intercostal pain is a common finding in tumors of neurogenic origin, varying from a slight twinge of pain to a severe neuralgia. The pain may be pleuritic in character, being aggravated by respiration. With involvement of the cardiac nerves, an anginal type of pain may be produced. In fact, several of our patients had been treated for a number of years for angina pectoris and had their activities markedly curtailed because of this diagnosis. Erosion of the vertebra produces a boring type of interscapular pain which is very severe. Invasion of the brachial plexus causes severe pain in the upper extremities. "Dumbbell tumors" of the spinal cord and mediastinum may exhibit symptoms and signs of spinal cord pressure.

Other neurological symptoms include hoarseness due to paralysis of the recurrent laryngeal nerve from pressure on this structure. Hiccups may be present as a result of phrenic nerve stimulation, although this is rare. The finding of Horner's syndrome (myosis, enophthalmos, and ptosis of the eyelid) will point to involvement of the cervical sympathetics. Vomiting may result from vagal nerve stimulation although this is usually a result of other factors.

Respiratory: Respiratory symptoms are the next most important group of symptoms which are the direct result of pressure of the tumor mass on some portion of the respiratory tract. Dry cough is usually noticed first, followed by the expectoration of sputum. The sputum is first mucoid but may become purulent, if obstruction to a bronchus exists and secondary infection supervenes. Pressure on a main bronchus or trachea results in wheezing, not unlike bronchial asthma. This is distinguished by the fact that it is often unilateral and is heard best on inspiration. Pressure over the trachea results in a coarse rhonchus and stridor. The brassy cough may also be the result of recurrent laryngeal paralysis. Dyspnea, which is mild at first, increases with increase in the size of the tumor and resultant decrease in vital capacity. Shortness of breath may occur with sudden onset, as with lobar pneumonitis, with no premonitory symptoms. Tumor may be suspected only when roentgenographic examination reveals a persistent shadow following subsidence of the pneumonia. Hemoptysis occurs in 20 per cent (5) of all mediastinal tumors. The hemoptysis results from the erosion of a blood vessel in the respiratory tract or secondary infection. Hemoptysis, secondary to a tumor of the mediastinum, is the fourth most common cause of pulmonary hemorrhage, being superseded in frequency only by tuberculosis, bronchogenic carcinoma, and bronchiectasis (5). Dyspnea is a prominent symptom of most mediastinal tumors of any magnitude.

Gastro-intestinal: Gastro-intestinal symptoms result primarily from pressure on the esophagus. Thus, difficulty in swallowing and a sensation of "sticking of food" in the gullet are the symptoms most commonly observed. The esophagus may be displaced considerably and only moderate obstruction result, provided there is no interference with the esophageal peristaltic waves. The occurrence of dysphagia is a serious symptom, which may mean carcinoma of the esophagus, and so is an indication for immediate and thorough investigation of the cause, Regurgitation of food occurs when the obstruction is nearly complete. Vomiting, however, is usually a symptom of advanced mediastinal malignancy and is not often seen in the benign cases.

Vascular: Obstruction of the great vessels in the mediastinum, although rarely observed in benign tumors of the mediastinum, is a common finding in malignant mediastinal tumors. This symptom represents a poor prognostic sign. In the superior mediastinum, the veins are compressed first and show dilatation on exercise or bending over. As the obstruction of the superior vena cava progresses, cyanosis of the head and neck occurs with associated pounding in the head, headache, and tinnitus. Marked dilatation of the veins, edema of the head and neck and extremities represent advanced venous obstruction. The development of collateral circulation in the chest wall parallels the venous obstruction. Pressure on the inferior vena cava is less common. When this vein is obstructed, edema of the legs and ascites develop. Progressive venous obstruction due to a mediastinal tumor almost always means a malignant tumor. Occasionally, an inflammatory lesion may produce a venous obstruction, but these cases are rare.

Miscellaneous: Fever is usually not a symptom of mediastinal tumor unless there is secondary infection in the lung due to pressure occlusion of the tracheobronchial tree. It is present in advanced malignancies, in some instances due to the breakdown of the tumor. The loss of weight and strength, secondary anemia, are evidence of advanced malignancies, but are less common than with malignant tumors found elsewhere in the body because of earlier deaths from compression of vital mediastinal organs. Marked loss of weight is usually secondary to esophageal obstruction. It is surprising how large benign mediastinal tumors may get without producing marked symptomatology.

PHYSICAL EXAMINATION

Early in the course of development of a mediastinal tumor there are few demonstrable physical signs. On palpation, tracheal deviation may be noted. Horner's syndrome and unilateral flushing point to involvement of the cervical sympathetic nerves. On percussion, the anterior or posterior mediastinum may be widened. The changes noted on auscultation in most instances depend upon the amount of obstruction to the trachea or bronchi present. Tenderness of the chest wall may be noted over the tumor. The development of herpes zoster would suggest the existence of intercostal neuritis from pressure on the affected nerve. In most advanced cases the signs of vascular obstructions are very spectacular. The distended neck veins, cyanosis and swelling of the neck, and dilatation of the capillaries on the chest wall usually point to the mediastinal obstruction of an extensive malignancy.

DIAGNOSTIC PROCEDURES

Roentgen examination: The roentgen examination is the most important diagnostic aid for the identification of mediastinal tumor. In addition to the conventional postero-anterior view, lateral and oblique films show the location on the anterior posterior plane. Fluoroscopy and roentgen kymography are useful in distinguishing between the transmitted pulsation and the intrinsic expansile pulsation found in aneurysms of the great vessels. In the case of an aneurysm with rigid walls, however, or one filled with laminated clot, no pulsation may be noted. Body section radiography (planograms, tomograms, laminograms, et

cetera) both in the postero-anterior and lateral planes often tells the exact point of attachment of the growths and their effect on adjacent organs. If no expansile pulsation is present in the aneurysm, the distinguishing of an aneurysm from a mediastinal tumor may be extremely difficult. Seldom, indeed, does an aortic aneurysm develop in a person in whom all serologic tests for syphilis are negative. The injection of 70 per cent diodrast into the median or cephalic vein will frequently reveal the presence of the suspected aneurysm. In some instances, to show the arch and the descending portions of the aorta, a retrograde carotid injection must be made. This technique clearly outlines the arch and descending aorta and is most helpful when aneurysms of the arch or of the descending aorta are suspected. In posteriorly located tumors, barium study of the esophagus shows possible changes in the esophagus effected by the tumor. Similarly, bronchograms will demonstrate any bronchial distortion resultant from pressure of a mediastinal neoplasm.

Endoscopy: Bronchoscopy is an important diagnostic procedure when the suspected mediastinal tumor is in such a position as to press upon the trachea or major bronchi. By endoscopic examination the amount, if any, of external compression on the trachea or bronchus, or occlusion from a neoplasm within these organs, can be accurately determined. The mobility and presence of inflammation of the bronchial walls will be accurately observed. The most important role of bronchoscopy, however, is the identification or exclusion of the primary bronchogenic carcinoma. This most common intrathoracic neoplasm may simulate tumor of the mediastinum. Early radical removal of bronchogenic carcinoma has proved the only successful cure. Thus, bronchoscopy always should be performed when bronchogenic carcinoma is a possibility. It should be emphasized that bronchoscopy is not indicated in all cases of tumors of the mediastinum. In posteriorly located tumors, those near the anterior chest wall, and those adjacent to the diaphragm, bronchoscopy is not necessary.

Esophagoscopy is indicated only in posteriorly located tumors where there is a possibility of esophageal involvement with the tumor. A carefully performed barium esophagram should be done first. No esophagoscopy should be performed unless there is definite evidence of changes in the contour of the esophageal shadow. In this instance too, carcinoma of the esophagus is the most serious condition to be discovered. The obstruction symptoms are usually paramount, however, and point to pathologic changes in the esophagus long before a mass or shadow is visible on the plain chest roentgenogram.

Diagnostic pneumothorax: Diagnostic pneumothorax was popular a decade ago to distinguish between intra- and extrapulmonary tumors. It was used not only as a diagnostic measure but also to collapse the lung preparatory to performing a lobectomy or pneumonectomy. Actually the preliminary pneumothorax prior to lung resection has been found of minimal value. The diagnostic worth of the pneumothorax is limited in the presence of intrapleural adhesions and often fails to point out the site of origin of the tumor. The more accurate procedure is the exploratory thoracotomy, which is to be preferred to diagnostic pneumothorax. In rare instances diagnostic pneumothorax may be employed. With a pneumo-

thorax established, thoracoscopic examination may be helpful in arriving at a diagnosis. The frequently restricted manipulation of the thorascope, however, and the presence of a small pneumothorax pocket make this procedure of limited value. At the best it is greatly inferior to surgical exploration.

Aspiration of tumor cells: The recovery of tumor cells by means of a needle introduced through the intact chest wall is warranted occasionally. Only when there is a question of the presence of localized pleural fluid or when a tumor, if malignant, is obviously inoperable, is aspiration justified. It should not be used when the tumor is located anteriorly for fear of tearing one of the great vessels. In tumors located posteriorly or laterally located tumors of great size, aspiration may be employed. We do not believe that it is justified to aspirate a tumor preoperatively in a case where operation is clearly indicated solely to determine the cell type. One of our cases with a huge teratoid tumor of the mediastinum was treated as a case of tuberculous empyema. Finally the aspiration of hair by thoracentesis showed a dermoid to be present.

Tests for specific granuloma: The exclusion of aneurysm of the aorta is probably one of the most important points in differential diagnosis of tumors in the vicinity of the aorta. The performance of serologic tests for syphilis on specimens of blood or cerebrospinal fluid is an important diagnostic procedure not to be omitted. Tuberculin tests and examination of the sputum for tubercle bacilli should be employed if tuberculosis is suspected. Tests for coccidiodes and ecchinococcus disease and other specific granulations also may be of value.

Trial X-ray therapy: One of the most helpful diagnostic tests is the use of deep X-ray therapy in possible cases of Hodgkin's disease and the lymphoma-lymphosarcoma group. The prompt shrinkage of an anteriorly placed perihilar or hilar mass after the administration of a skin dose of from 750 to 1,000 r. usually means a tumor of this group. This test represents a satisfactory diagnostic procedure because no other intrathoracic lesion is so radiosensitive. Furthermore, since no benign lesion is radiosensitive, the decrease in size of the tumor, as seen on the roentgenogram following this therapy, represents a contraindication to operation. Prolonged and extensive deep X-ray treatment should be discontinued if there has been no shrinkage in the size of the tumor after three or four weeks. Prolonged roentgen therapy will not only be ineffectual but also it may make the surgical removal of a benign tumor very difficult. If a mediastinal lesion primarily held to be malignant does not definitely decrease in size following radiation therapy, the patient should be explored at once.

Biopsy: Biopsy of accessible peripheral lymph nodes is always in order in any part of the body where the diagnosis of metastatic malignancy in lymph nodes is suspected. Mediastinal tumors present no exception to the rule. For the finding of malignant metastasis contraindicates surgical exploration.

Surgical exploration: This procedure is often the only certain means of establishing the diagnosis of a benign mediastinal tumor. If, after a careful analysis of the various tests outlined above, the diagnosis is in question, surgical exploration is indicated, provided the patient is a suitable subject for surgery. A more complete discussion of exploratory thoracotomy is presented later.

Comparison of symptoms of benign and malignant mediastinal tumors and certain differences between benign and malignant tumors is outlined in table 2.

The malignant tumors produce local and constitutional symptoms which are invariably progressive. It is only when the benign tumors become very large or press upon "sensitive" organs that comparable symptoms are noted. Obstruction of the great vessels and the rapid development of collateral circulation on the chest wall is almost invariably a sign of a malignant lesion of the mediastinum.

LOCATION OF VARIOUS TUMORS

It is impossible to catalogue the location of all of the types of mediastinal tumors because of the lack of accumulated evidence on the rarer types and the differences of opinion regarding tumor location in the literature. This difference of opinion undoubtedly is based upon varied sites of origin for these neoplasms.

TABLE 2

Comparison of the Symptoms of Benign and Malignant Mediastinal Tumors

BENIGN	MALIGNANT
1. Slow growth	Rapid growth
2. Usually unilateral	Often bilateral
3. Few constitutional symptoms	Marked constitutional symptoms
4. No pleural effusion	Pleural effusion frequent
5. Superior vena cava obstruction rare	Superior vena cava obstruction frequent
6. Peripheral nodes not enlarged	Peripheral nodes enlarged
7. Nerve paralysis rare	Nerve paralysis frequent
8. Pulmonary tissue compressed	Pulmonary tissue invaded
9. Border smooth and circumscribed	Border frequently irregular
10. No response to X-ray therapy	Lymphoid tumors respond

Nevertheless, it is worth while to point out the more usual location of the commoner types of mediastinal neoplasms as diagrammed in figure 3. It will be noted that neurogenic tumors, esophageal and gastroenteric cysts occupy a posterior location although the latter may present in the middle mediastinum. Bronchogenic cysts, although attached centrally, may present in either an anterior or posterior position. Lymphoid tumors involving the lymph nodes, such as the lymphoma, Hodgkin's, lymphosarcoma group are commonly found comparatively early in their development in an anterior or central position. Metastatic malignancies, teratoid tumors, thymic tumors, intrathoracic goiter, pericardial cysts, and possibly lipoid tumors develop in an anterior location. This leaves a very large group of rarer types of mediastinal tumors for which greater experience will be needed in order that they may be accurately located. It is true also that exceptions to the locations of the various tumors shown in figure 3 may be found. Nevertheless, it is believed that this diagram will be helpful in the majority of the cases in locating the types of neoplasms depicted in the diagram.

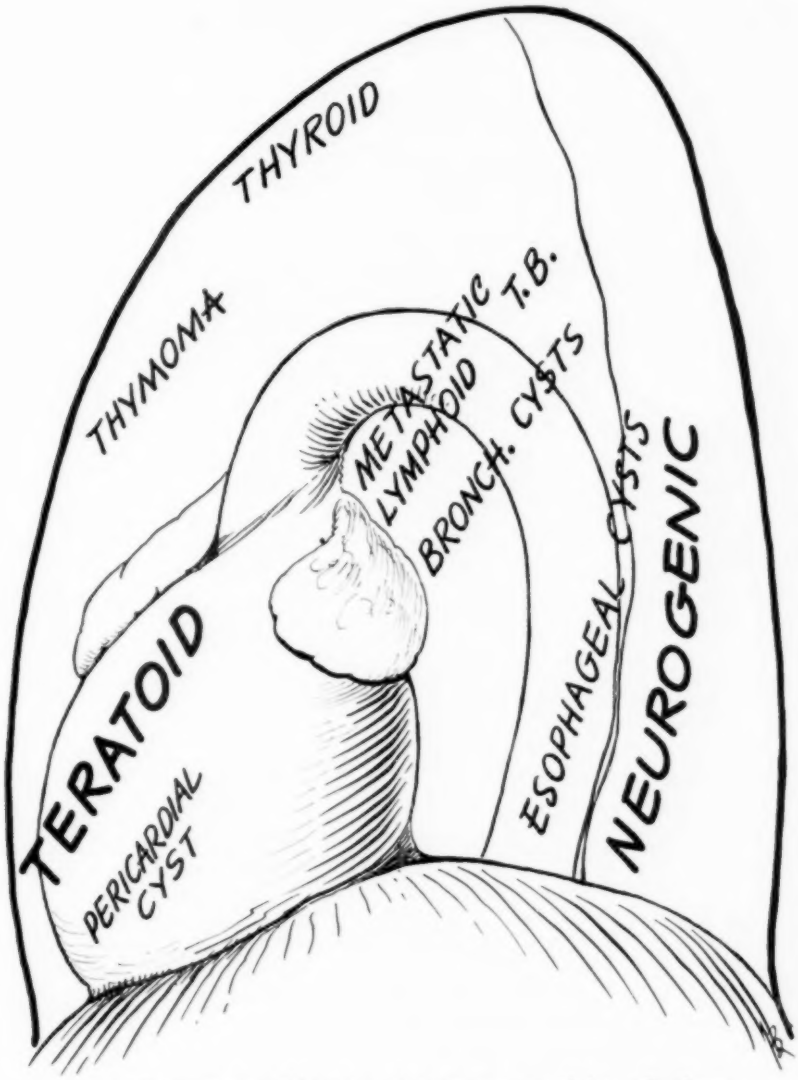


FIG. 3. Diagrams of usual locations of common tumors of the mediastinum.

DIFFERENTIAL DIAGNOSIS

A list of conditions commonly confused with mediastinal tumors is presented in table 3. Bronchogenic carcinoma is the most common intrathoracic tumor. It

is resistant to X-ray therapy, and surgical excision before spread has occurred is necessary to effect a cure. It is most important to distinguish this bronchogenic carcinoma from mediastinal tumor. In carcinoma of the lung arising close to the hilum, the shadow is usually irregular at the periphery. Bronchoscopy is frequently positive and the cancer cells may be found in the sputum. Cough, expectoration, and blood spitting are more common. However, in the superior sulcus tumor, now known to be a form of bronchogenic carcinoma in the great majority of cases, pain in the shoulder or arm, Horner's syndrome, and slight cough are present. It is extremely difficult to distinguish this lesion from a superior mediastinal tumor. If the tumor mass presents a smooth outline, it is likely to be a benign mediastinal tumor, and operation is indicated. If the borders are irregular, however, or there is evidence of invasion of adjacent tissues, we should suspect either a superior sulcus bronchogenic carcinoma or a malignant mediastinal tumor, both of which are usually inoperable by the time the diagnosis is made. If the presence of carcinoma of the lung cannot be excluded in

TABLE 3

Conditions which Simulate Mediastinal Tumors

1. Carcinoma of lung
2. Benign tumors of lung
3. Cysts of lung
4. Aneurysms of heart and great vessels (dissecting aneurysms)
5. Chest wall tumors
6. Tuberculosis of mediastinal lymph nodes
7. Hydatid disease
8. Mediastinal abscess
9. Thrombosis of superior vena cava
10. Diaphragmatic hernia

the differential diagnosis of a possible mediastinal tumor, and no evidence of spread of the cancer can be found, surgical exploration is definitely indicated provided the condition of the patient permits this procedure.

Benign tumors of the lung occurring close to the hilum, if they occlude a major bronchus, usually produce atelectasis of the lung before they reach sufficient size to present a mediastinal mass on roentgen examination. They are readily diagnosed at bronchoscopy. If the main or branch bronchus is not occluded, however, it may be very difficult to distinguish between the two conditions. In most instances bronchial adenomas close to the hilum can be seen at bronchoscopy. Pulmonary cysts located close to the hilum, if filled with fluid, are indistinguishable from benign tumor of the mediastinum. Since operation is indicated for both of these lesions, the failure to distinguish between these conditions is not serious. Chest wall tumors located close to the sternum or spine often present a palpable mass. They frequently cause pain, but little, if any, pulmonary symptoms. Planigrams are helpful in showing their point of origin. Since they are potentially malignant, excision at the thoracic wall is indicated.

Aneurysms of the heart and great vessels present a difficult problem in differ-

ential diagnosis. Until the various surgical methods to treat aneurysms are perfected, thoracotomy for aneurysms is not indicated. When the mediastinal mass shows expansile pulsation and the Wassermann test is positive, a syphilitic aneurysm is the most likely diagnosis. However, a nonpulsile aneurysm or one with a laminated clot may only be diagnosed by the contrast arteriography with injection of diodrast. In some instances aneurysm will be only diagnosed at exploratory thoracotomy. Dissecting aneurysms are particularly difficult to diagnose, as they increase in size and cause pain similar to an invasive mediastinal tumor.

Thrombosis of the superior vena cava is a very rare condition. It is manifested by the signs of superior vena cava obstruction without the finding of enlargement of the mediastinum suggestive of a tumor on roentgen examination.

Enlarged mediastinal lymph nodes due to pulmonary tuberculosis usually contain calcium deposits. The tuberculin test is positive and there may be signs of healed pulmonary tuberculosis on the chest roentgenogram. Only occasionally will there be confusion with mediastinal tumors. The location and calcification of these nodes is usually diagnostic. They are mainly asymptomatic and should be left alone. A few have been removed according to certain reports of the medical literature; however, there is rarely indication for their excision.

Hydatid disease is not common in the United States and only when it is present in the lung adjacent to the mediastinum will mediastinal tumor be simulated. The precipitin test and skin tests are positive in high titers with an active hydatid cyst. Often hooklets may be recovered from the sputum.

Mediastinal abscess, though presenting a widening of the mediastinal shadow on roentgen examination, will rarely be confused with neoplasm of the mediastinum. Usually there is history of trauma, foreign body in esophagus, instrumentation, et cetera. High fever, tachycardia, dyspnea, great weakness, and prostration usually come on rapidly. Thus the signs and symptoms of an acute infection are paramount. The development of a fluid level in the mediastinum is diagnostic of a mediastinal abscess. Intensive antibiotic therapy and prompt surgical drainage are indicated.

Diaphragmatic hernia is usually diagnosed by a careful upper gastro-intestinal roentgen study. However, if the herniated sac contains only omentum and not a portion of the stomach or intestines, then a tumor of the mediastinum will be simulated. We have operated upon two such cases in our series.

TYPES OF MEDIASTINAL TUMORS

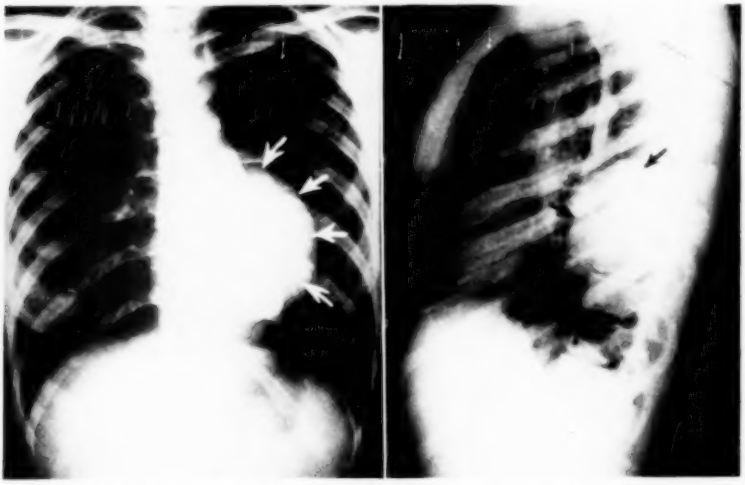
In table 4 are recorded the various types of mediastinal tumors found in our series. Neurogenic tumors were most common, while teratoid tumors were second and cysts third in frequency. Blades (3) also found primary nerve tumors most frequent, with bronchogenic cysts second; teratoid tumors third; and pericardial cysts fourth. These groups of mediastinal tumors make up three-fourths of the benign tumors that are subjected to surgery. A miscellaneous group is included in the remainder. The malignant mediastinal tumors operated upon are few in

number and so varied in type as to prevent cataloging. The salient characteristics of the most common benign mediastinal tumors are presented.

TABLE 4

Types of Mediastinal Tumors in Writers' Series

BENIGN		MALIGNANT	
Neurogenic tumors	16	Sarcoma	5
Teratoid tumors	8	(a) Spindle cell	2
Cysts	5	(b) Fibroblastic	1
(a) Bronchogenic	3	(c) Lipo	1
(b) Pericardial	2	(d) Neuro	1
Thymoma	2	Hodgkin's	3
Thyroid	2	Endothelioma	1
Leiomyoma	1		
Cystic hygroma	1		
Totals	35		9



FIGS. 4 and 5. Neurofibroma of posterior mediastinum. A 23-year-old secretary had a chest film taken as part of a mass survey for pulmonary tuberculosis at the state fair. Tumor mass discovered.

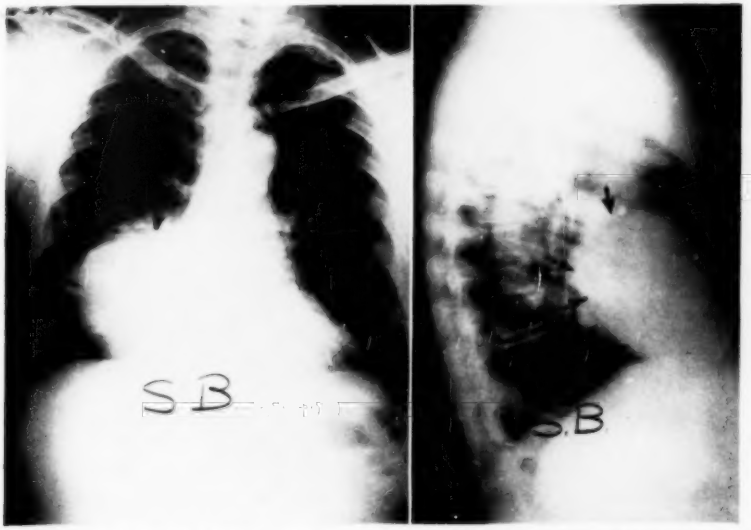
FIG. 4. (Left) Posterior anterior view of chest shows sharply circumscribed ovoid soft tissue mass behind cardiac shadow.

FIG. 5. (Right) Lateral projection demonstrates tumor to lie posteriorly next to spine. After film was taken, patient admitted she had some left chest pain. Benign neurofibroma removed at thoracotomy performed through posterolateral approach. Patient now well.

Neurogenic tumors: Primary nerve tumors represent one of the three most common types of mediastinal tumors and are the most important growths of the posterior mediastinum. Neurofibroma, neuroblastoma, ganglioneuroma,

et cetera, may be found. In 1940 Heuer and Andrus (6) collected 108 cases of these tumors and in 1944 Heuer, Kent, *et al.* (7) reviewed 105 collected cases, including 18 from Barnes Hospital. Most neurogenic tumors are relatively asymptomatic. Dull intercostal pain, not regarded as being important by the patient, is usually the first early symptom.

Several of the cases in our series were discovered quite accidently in persons who considered themselves to be well but who, on further questioning, admitted



FIGS. 6 and 7. Teratoid tumor of anterior mediastinum. A 55-year-old engineer complained of cough, dyspnea, and pain in right anterior chest of twenty years' duration. X-ray therapy given fifteen years previously without relief.

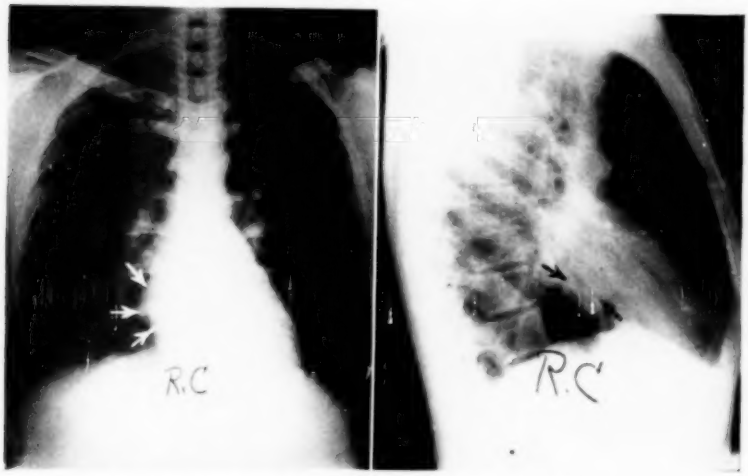
FIG. 6. (Left) A round sharply circumscribed homogenous mass, as dense as the cardiac shadow, is seen protruding from the right mediastinum, resting on the diaphragm on the posterior anterior film.

FIG. 7. (Right) Later view reveals this rounded mass to have an anterior location. A benign teratoma of the anterior mediastinum was removed by a thoracotomy performed through the posterolateral approach. Patient is now well and working.

slight chest pain. Horner's syndrome in one case proved to be evidence of a neuroganglioma, although the various types of nerve tumors cannot be distinguished clinically. When clinical signs and symptoms of moment are noted, most often malignant changes have taken place. This occurs in 37 per cent of the cases (7). Roentgen examination shows a characteristic shadow, smooth in outline, which may be lobulated and is of moderate soft tissue density, sharply circumscribed in the posterior mediastinum (figures 4 and 5.) A careful search for erosion of the vertebrae should be made for this is strongly suggestive of intraspinal extension of the tumor in a dumb-bell-like configuration. Neurogenic

tumors do lend themselves to surgical removal in the benign state. Since approximately one-third of them become malignant, they should be removed as soon as diagnosed, even though asymptomatic.

Teratoid tumors: The group of teratoid tumors includes both the dermoids and teratomas, of which the latter are most common according to Harrington (8). Teratoid tumors are the most frequent benign neoplasms of the anterior mediastinum, 251 cases having been collected (9). These tumors grow slowly and



FIGS. 8 and 9. Bronchogenic cyst of mediastinum. A 36-year-old male accountant complained of hemoptysis and a "tumor in the lungs." Patient had known rheumatic heart disease, completely compensated. Bronchoscopy showed some distortion of the right lower lobe bronchus.

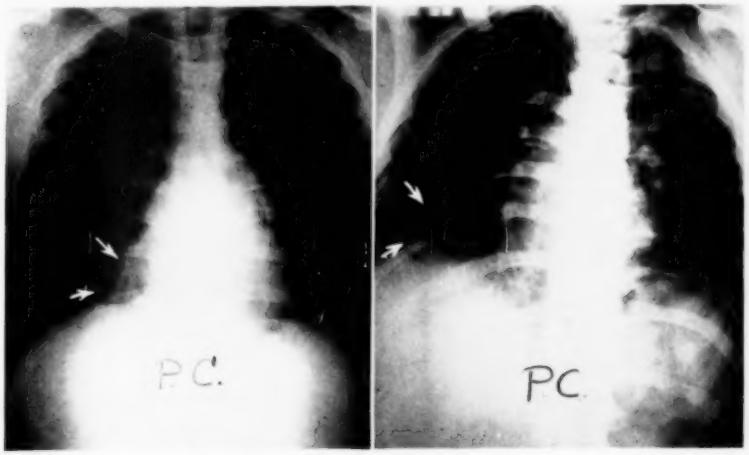
FIG. 8. (Left) Small circumscribed mass projecting from the lower right mediastinum is seen on posterior anterior film.

FIG. 9. (Right) A sharply circumscribed mass of central mediastinum is partially obscured by the cardiac shadow. Preoperative diagnosis: either adenoma of bronchus or mediastinal tumor. A benign bronchogenic cyst of the mediastinum was removed. Postoperative course uneventful. It is questionable whether this cyst was responsible for hemoptysis.

rarely present symptoms before puberty. Intermittent cough, respiratory infections, and thoracic pain are the common symptoms. Hair may be coughed up when erosion has occurred in the bronchial tree, or it may be aspirated by a needle introduced through the chest wall. In some instances the tumors may have a cervical extension. Roentgenologic examination shows a dense, smooth, round tumor usually in the anterior mediastinum; occasionally an irregular border is seen (figures 6 and 7). Several cases have been reported in the posterior mediastinum. If teeth or bone are present, there is no question about the diagnosis. Teratoid tumors have been found to be malignant, 12.9 per cent of the cases (9). Once malignant change has taken place and invasion of structures contiguous

to the tumor has developed, the chance of cure by any method of treatment is exceedingly remote. Surgery of the benign teratoid tumors has been very successful, while X-ray therapy has shown little beneficial effect. It is obvious, therefore, that early surgical removal is urgently indicated.

Bronchogenic cysts: Cysts of bronchogenic origin are uncommon. Blades (3) found 35 cases in the literature up to 1946 and added 23 additional cases in his collected series from Army medical centers. Bronchogenic cysts may arise from any point along the tracheobronchial tree and be present in either the anterior or posterior mediastinum. Cough and substernal discomfort are the usual complaints



FIGS. 10 and 11. Pericardial cyst. A 44-year-old dentist complained of pain in the right anterior chest for several years.

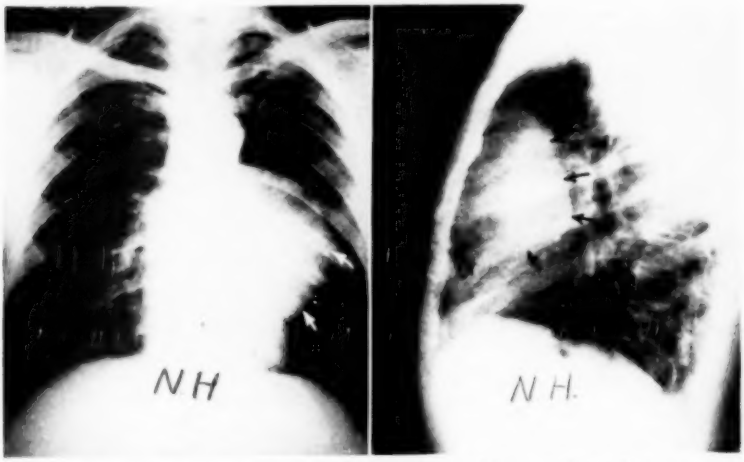
FIG. 10. (Left) The posterior anterior chest film demonstrated an oval homogenous shadow blending with the cardiac silhouette at the level of the diaphragm.

FIG. 11. (Right) Oblique film reveals shadow to be anterolateral in location, extending outward from the cardiac outline. A pericardial cyst was removed by thoracotomy performed through a posterolateral approach. Patient is well and free of symptoms.

and the signs of infection may be present. In most instances the cysts are entirely asymptomatic and are discovered only on routine chest films. On the roentgen examination they appear as rounded or oval masses often in either the anterior or posterior mediastinum (figures 8 and 9). The shadow may be ill-defined on the lateral view. Fluoroscopy often reveals movement of the mass on swallowing, due to the attachment to the trachea for upper mediastinal cysts. These cysts are insensitive to X-ray therapy. If infected, there is no question about their removal. If asymptomatic, their removal is necessary because of the difficulty in distinguishing these lesions from teratoid tumors and bronchogenic carcinoma, where excision is definitely indicated.

Pericardial cysts: Cysts of the pericardium have been reported in the literature in only 21 cases. Though usually asymptomatic, slight anterior chest pain

was noted in the 2 cases in our series. These cysts present in the anterior mediastinum as circular or oval masses which are less dense than teratoid tumors, and on fluoroscopy are definitely attached to the pericardium (figures 10 and 11). Roentgen therapy is ineffectual in reducing the size of the cyst. The true diagnosis can only be made by exploratory thoracotomy, at which time the removal is technically a simple procedure. Operative intervention is indicated, therefore, to rule out more serious types of mediastinal and pulmonary tumors for which surgery is the only hope.



FIGS. 12 and 13. Thymoma. A 55-year-old rancher had increased cough, expectoration, and dyspnea for several years.

FIG. 12. (Left) Posterior anterior film of the chest shows a slightly lobulated homogenous mass extruding out from the left lateral border of the heart.

FIG. 13. (Right) On the lateral projections a lobulated shadow is present in the anterior mediastinum, overlying but distinct from the heart shadow. Bronchoscopy showed displacement of left main bronchus. Penicillin therapy given for three weeks before operation because of chronic bronchitis. A large thymoma of the anterior mediastinum was removed through the posterolateral approach. Patient is much improved and now working. Residual cough is present, probably on basis of low grade bronchiectasis, secondary to prolonged bronchial obstruction from the benign mediastinal tumor.

Thymus: The vast majority of thymic tumors are malignant, several hundred having been reported in the literature (10). We are excluding those thymic tumors found in association with myasthenia gravis, for this latter disease so dominates the clinical picture as to present problems not pertinent to this discussion. It seems worthwhile, however, to comment on the two benign cases in our series. Both had substernal distress and cough as predominating symptoms. More often benign thymomas are asymptomatic. Roentgen examination reveals a mass in the anterior mediastinum in the region of the thymus which is fairly dense, but exhibits no particular characteristics (figures 12 and 13). It cannot

be distinguished from lymphoid tumor of the mediastinum. If X-ray therapy is ineffectual, removal is indicated since the great majority of thymic tumors undergo malignant degeneration.

Miscellaneous benign tumors: The other benign tumors in our group of cases included thyroid, leiomyoma of the esophagus, and cystic hygroma. We have not encountered such rare neoplasms as gastro-enteric cysts, hemangiomas, fibromas, xanthomas, et cetera. The reader is referred to the excellent recent collective review of the literature compiled by Thompson (11) in 1947 as well as the earlier reports of Heuer and Andrus (8), Bradford, *et al.* (2), Blades (3), and others.

MALIGNANT TUMORS

Only 9 malignant neoplasms were operated upon in this series. In at least four times that number of cases we were able to make this diagnosis of malignant mediastinal tumor without operation, so that no surgery was done. In 5 instances some type of sarcoma was found; in 3 cases Hodgkin's disease was the diagnosis; while the final case was proved to be an endothelioma. No one of these cases was cured by surgery as it was impossible to remove completely these malignant tumors because of invasion of vital structures.

INDICATIONS FOR SURGICAL OPERATIONS

It is now generally agreed that all benign mediastinal tumors should be removed by surgery (1, 2, 3, 6, 11, 12). This plan of treatment is based on the fact that benign mediastinal tumors are potentially malignant. To remove them when they are present as discrete circumscribed tumors is to take advantage of a golden opportunity to cure the patient. In waiting until marked symptoms are present, the one chance to effect a cure may be permanently lost. Furthermore, some benign mediastinal tumors may become so large as to seriously interfere with pulmonary and cardiac function; with continued growth, death supervenes even though no actual malignant change has taken place. The surgical excision of benign mediastinal tumors when severe cardiopulmonary symptoms have developed is often difficult and the results less certain. In some instances pulmonary tissue has been compressed and destroyed by secondary infection, so that lobectomy or pneumonectomy must be performed as well. The risk of operation for early cases is very small and should be less than 3 per cent with qualified anesthetists and surgeons. The chances of cure are practically 100 per cent when a discrete benign mediastinal tumor can be removed completely.

On the other hand, surgery is not indicated for most malignant mediastinal tumors. Rarely a malignant tumor may be removed before extensive metastasis has occurred. As has been stated, tumors of the lymphoma group uniformly respond to deep X-ray therapy. With experience the roentgenologist and the surgeon will be able to tell in most instances which cases should have a test dose of roentgen therapy. We do not now advocate, by any means, the routine use of X-ray therapy in all cases of mediastinal tumor, although we formerly held this

view (12). However, if there is no response to the X-ray treatment in three or four weeks' time, then surgery should be promptly undertaken. To prolong the roentgen treatments after an adequate test dose has been administered results in no benefit to the patient. The removal of a benign lesion will be rendered more difficult and hazardous and the result, therefore, less certain. When there is not definite evidence of a malignant neoplasm of the mediastinum and X-ray therapy has failed, surgical exploration is then indicated.

SURGICAL TREATMENT

Our early cases were operated upon without the benefit of antibiotics. However, the last 22 patients in this series received penicillin routinely on the day before surgery and for one week thereafter. In several instances the presence of severe chronic bronchitis necessitated a longer preoperative administration of the drug. No postoperative pulmonary or pleural complications were seen with the use of penicillin. We prefer the posterolateral approach to the mediastinum to the anterior one, because a much better exposure of the pleural cavity is gained by this approach. Splitting of the sternum is feasible when an anterosuperior mediastinal tumor presents directly beneath the sternum in some instances. Endotracheal anesthesia is necessary. Most benign tumors of the mediastinum can be shelled out if one locates the proper plane of dissection. The operative technique must be meticulous with due regard for the important structures in the mediastinum. The large veins must be handled with great care, for they are easily torn in the dissection. This is especially true if considerable roentgen therapy has been employed. Because the blood supply of a mediastinal tumor is often great, care must be taken to identify the vascular trunks supplying the tumor, particularly aberrent arteries arising from the great vessels. Temporary water seal, catheter drainage, is employed for twenty-four to forty-eight hours. The usual postoperative precautions for any thoracotomy are employed to prevent postoperative pulmonary complications. The course after surgery is mild and usually the lung expands rapidly. Most of the patients may be discharged in one week to ten days.

RESULTS

No deaths occurred in this series of operated cases in which the cause of death could be attributed to the operation. In one patient death occurred two months after operation due to a spontaneous rupture of the esophagus in a case where a benign neurofibroma had caused necrosis of the esophageal wall. In a case of cystic hygroma extruding down from the neck to the mediastinum, the cell type was benign. It was impossible to remove the tumor completely. All other cases of benign mediastinal tumors were cured by the operation. In the malignant cases, recurrence of the tumor was the rule although several patients have been alive for several years following surgery. The prognosis of these patients is still poor.

SUMMARY AND CONCLUSIONS

Many mediastinal tumors are now being discovered by routine roentgen films of the chest. A definite plan of investigation has been presented for patients with

possible tumors of the mediastinum. This is based upon a proper evaluation of symptoms, physical signs, and specialized procedures. The specialized procedures consist of various roentgen studies (including the use of planograms and contrast media), endoscopy, test for specific granuloma, trial X-ray therapy, biopsy of accessible lymph nodes, and surgical exploration. By means of this plan of investigation it is possible to differentiate between benign and malignant mediastinal tumors and other intrathoracic lesions in most instances. The clinical and roentgen findings of the common types of benign mediastinal tumors has been discussed.

Since all benign mediastinal tumors are potentially malignant and X-ray therapy is ineffectual, surgical removal is definitely indicated. The golden opportunity for removal of a mediastinal tumor is presented when the lesion is discrete and the symptoms are absent or minimal.

X-ray therapy is effectual only for lymphoid tumors. In all other malignant tumors the chance of cure is very poor. Therefore, it is the responsibility of every physician to urge that the relatively asymptomatic benign mediastinal tumor be removed before malignant change develops. The risk of operation is slight and the percentage of cures is high.

SUMARIO

Tumores del Mediastino: Discusión del Procedimiento Diagnóstico y del Tratamiento Quirúrgico a Base de lo Observado en Cuarenta y Cuatro Casos Operados

Hoy día se descubren muchos tumores mediastínicos por medio de las radiografías corrientes del tórax. Para los enfermos en que existe tal posibilidad, preséntase un plan bien definido de investigación, basado en la justipreciación de los síntomas, signos físicos y procedimientos especializados. Los últimos comprenden varios estudios roentgenológicos (incluso empleo de planografías y medios de contraste), endoscopia, ensayo para granuloma específico, roentgenoterapia tentativa, biopsia de los ganglios linfáticos accesibles y exploración quirúrgica. Por medio de este plan de investigación, es posible diferenciar, en la mayoría de los casos, los tumores benignos y malignos del mediastino y otras lesiones intratorácicas. Discútense los hallazgos clínicos y radiológicos en las formas más comunes de los tumores benignos del mediastino.

Visto que todos los tumores mediastínicos benignos son potencialmente malignos y que los rayos X resultan ineficaces, la extirpación quirúrgica está netamente indicada. El momento óptimo para la excisión de un tumor del mediastino es cuando la lesión es discreta y no hay síntomas o éstos son mínimos.

Los rayos X sólo surten efecto en los linfomas. En todas las demás neoplasias malignas, bien pocas son las probabilidades de curación, por lo cual, a todos los médicos les corresponde la obligación de encarecer la extirpación de todo tumor mediastínico benigno y relativamente asintomático antes de aparecer alteraciones malignas. El riesgo que entraña la operación es leve y el porcentaje de curaciones elevado.

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THE URINARY EXCRETION OF AMINO ACIDS: I. BY NORMAL MALE SUBJECTS ON CONTROLLED LOW- AND HIGH-PROTEIN DIETS[1,2,3]

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INTRODUCTION

The purpose of this investigation was to compare the urinary excretion of amino acids of normal males with that of male subjects with moderately advanced tuberculosis. It was believed that such a study might provide new knowledge concerning protein deficiencies in the presence of an infection.

A definite relation has been established between hypoproteinemia and lowered resistance to infection, which is partially explained by Cannon (2) as an impaired capacity of animals to produce antibodies after their protein reserves had been depleted by artificial means. With this in mind, some clinicians (3) have given high protein diets to their tuberculous patients. It was found that the diets apparently increased muscle tone and decreased the period of hospitalization.

In preliminary experiments appreciable differences were found between the two groups, but it was considered desirable to repeat the experiments using rigidly controlled diets. The normal ranges of the urinary amino acids reported previously (4 to 10) have varied rather widely although they have provided a reasonable basis for clinical studies (11 to 13) of liver disease, cystinuria, and other disorders in which there were marked changes from the normal amino acid output.

EXPERIMENTAL

Data are reported in the present paper from experiments with normal male subjects maintained on fixed high- and low-protein diets of the caloric value. The daily food intake of each subject was adjusted to an amount equivalent to 1.36 Gm. of protein per Kg. of body weight on the high-protein diet and to 0.70 Gm. on the low-protein diet. The high-protein intake was the same as that of tuberculous patients at The Charles Cook Hastings Home. The low-protein intake was selected as that which, it was assumed, would maintain the subjects in nitrogen equilibrium.

Each of the 9 volunteer male subjects was maintained four days on the low-protein diet[4] and approximately 15 ml. of water per Kg. of body weight per day.

[1] From the Chemical Laboratory, University of California, Los Angeles, California, and The Charles Cook Hastings Home, Altadena, California.

[2] Paper 57. For Paper 56 see Camien and Dunn (1).

[3] This work was aided by a grant to one of us (M. S. D.) from the John and Mary R. Markle Foundation.

[4] The same food, cooked in the laboratory, was eaten at the same time by all subjects in quantities proportional to their body weights.

Twenty-four-hour urine samples were collected on the third and fourth days. All samples were preserved under toluene and were refrigerated. All of the subjects were moderately active during the experiments. The same 9 subjects were

TABLE 1

Composition of Low-protein Diets

(Gm. per 70 Kg. body weight)*

1		2	
Bread, white†	75-LD	Banana	100-D
Butter	30-BLD	Bread, white	75-LD
Cake, white with chocolate icing	87-L	Butter	60-BLD
Coffee cake with icing	70-B	Cake, white with chocolate icing	87-L
Corn, canned	100-B	Coffee cake with icing	70-B
Cream	65-BLD	Cream	50-BLD
Hamburger	32-D	Doughnut	50-D
Ice cream, vanilla	71-L	Fish, tuna	46-D
Lettuce	10-D	Ham, deveied	40-L
Mayonnaise	14-D	Ice cream, vanilla	71-L
Orange Juice‡	360-B	Lettuce	10-D
Peaches, canned	50-D	Mayonnaise	14-D
Peanut butter	30-L	Noodles, canned	120-D
Pudding, chocolate	100-D	Orange Juice	360-B
Sugar	20-BLD	Sugar	20-BLD
Spaghetti with tomato sauce	220-D	Tomato Juice‡	200-L
Tomato juice	200-L		

3			
Bacon	10-L	Jelly	30-D
Bread, white	75-LD	Lamb chop	55-D
Butter	40-BLD	Lettuce	10-D
Cake, white with chocolate icing	87-L	Mayonnaise	14-D
Coffee cake with icing	70-B	Orange juice‡	360-B
Cream	50-BLD	Pears, canned	50-D
Doughnut	50-D	Peas, canned	100-D
Eggs, boiled	50-L	Potato, baked	100-D
Ice cream, vanilla	71-L	Sugar	20-BLD
		Tomato juice	200-L

* Coffee, 135 ml. at each meal.

B, breakfast. L, lunch. D, dinner.

† 50 Gm. at L and 25 Gm. at D. Other foods taken at more than one meal divided uniformly.

‡ Half taken at 2:30 p.m.

maintained similarly on the high-protein diet. The composition of the low- and high-protein diets is given in tables 1 and 2.

The microbiological procedures and techniques were those described previously[5]. The solutions were compensated for NH_4Cl as well as NaCl. Urea was removed by urease

[5] The microbiological procedures employed are described in a paper by Dunn, *et al.*, Publications in Physiology, University of California Press, 1949, *8*, 293 to 326.

treatment from the unhydrolyzed urines containing amino acids (isoleucine, leucine, lysine, methionine, valine, and threonine) at relatively low concentrations. The mean deviations from the mean values for the different levels of samples averaged about 4 per cent for most of the assays. The microbiological data are given in tables 3 to 5.

RESULTS

It may be seen (table 3) that the total percentages of twelve amino acids determined in hydrolysates of representative samples of the high- and low-protein diets differed by a factor of approximately 2.4. It is also evident (table 3) that the proportions of the amino acids were different in the two diets. This unintentional variation in the quality of the dietary proteins illustrates the need of

TABLE 2

Composition of High-protein Diets

(Gm. per 70 Kg. body weight)*

Bacon	20-D	Ice cream, vanilla	72-L
Beans, string	75-L	Lettuce	30-LD
Beef, roast	60-L	Milk, homogenized¶	960-BLD
Bread, white†	75-LD	Orange juice‡	360-B
Butter	20-BLD	Peaches, canned	50-L
Carrots	20-D	Pears, canned	50-D
Cake, white with icing	50-D	Potato, baked	70-L
Celery	20-L	Soup, chicken noodle canned	120-D
Corn flakes	15-B	Strawberries, frozen	30-L
Cottage cheese	30-D	Sugar	10-BLD
Crackers	10-§	Toast, whole wheat	25-B
Cream	100-BLD	Tomato	40-D
Eggs, fried	100-B		

* Coffee, 65 ml. each meal.

B, breakfast. L, lunch. D, dinner.

† 50 Gm. at L and 25 Gm. at D. Other foods taken at more than one meal divided uniformly.

‡ Half taken at 2:30 p.m.

§ Taken at 8:00 p.m.

¶ One-fourth taken at 8:00 p.m.

dietitians for accurate information on the amino acid composition of different dietary protein sources[6].

Both hydrolyzed and unhydrolyzed urine samples were studied in the present investigation because of the possibility that results obtained on unhydrolyzed samples may be of clinical importance (when compared with levels determined on unhydrolyzed samples from pathological cases). It is recognized, however, that amino acid values determined microbiologically in unhydrolyzed urine do not represent values for "free amino acids" or for any other (at present) definable entities. For convenience, values found for unhydrolyzed urines have been reported as "amino acid" values in the present paper. It should be qualified,

[6] The diets were calculated by Emma J. Hollett, dietitian of the Charles Cook Hastings Home.

therefore, that these values (for unhydrolyzed urine) refer only to resultant activities from unknown mixtures of amino acid complexes and free amino acids. Although it is evident that acid hydrolysis greatly reduces the possible number of substances which may have variable amino acid activity, some compounds closely related to the amino acids (perhaps the corresponding hydroxy and keto acids) may be present, even in hydrolyzed urine. It is important, therefore, that analytical methods of the highest possible specificity be selected for the study of such samples. That the microbiological methods probably are more specific than the chemical methods which have been applied to urine has been pointed out by some workers (15).

TABLE 3

*Dietary Amino Acids**

AMINO ACID	GM. CONSUMED PER DAY		PER CENT OF TOTAL DETERMINED		PER CENT DIFFERENCE†
	Diet IA	Diet II	Diet IA (B)	Diet II (C)	
Arginine	1.56	4.24	4.7	5.3	13
Aspartic Acid	4.62	8.92	14.0	11.0	−21
Glutamic Acid	11.0	20.7	33.0	26.0	−21
Glycine	1.36	4.04	4.1	5.0	22
Histidine	0.90	2.44	2.7	3.0	11
Isoleucine	2.00	5.76	6.1	7.2	18
Leucine	3.10	8.88	9.4	11.0	17
Lysine	1.92	7.36	5.8	9.2	59
Methionine	0.80	2.20	2.4	2.7	12
Phenylalanine	1.84	4.68	5.6	5.8	4
Threonine	1.70	4.80	5.2	6.0	15
Valine	2.16	6.24	6.6	7.8	18
Total	32.96	80.22	100.0	100.0	

* One-tenth the quantity of each food component (except coffee and sugar) consumed daily per 70 Kg. subject was taken, the aliquots were mixed with 300 ml. of 12 *N* HCl and the mixture was refluxed for 20 hours. The amino acids were determined by microbiological assay.

† $[(C) - (B)] \times 100/(B)$.

The daily output (hydrolyzed urines) of each amino acid per individual was nearly constant on two successive days for each of the fixed diets (table 5). The values for 12 amino acids and 9 subjects differed from the means by approximately 5 per cent on the low-protein diet and by approximately 6 per cent on the high-protein diet. The comparable values for amino acids in unhydrolyzed urines were each approximately 10 per cent (table 4). That the latter values were somewhat larger than the former was not unexpected because of the probability that the proportions, as well as the microbiological activities, of metabolites in unhydrolyzed urines would be variable.

The excretion (hydrolyzed urines, table 5) of each amino acid by the different individuals deviated from the mean values by 9.0 (3.7 to 17.4) per cent on the

low-protein diet and by 13.5 (6.3 to 19.6) per cent on the high-protein diet. This degree of inconsistency may indicate a normal variation between adult males in the utilization and excretion of amino acids. In general, the excretion (hydrolyzed urine) of amino acids on the rigidly controlled high-protein diet

TABLE 4

*Amino Acids in Unhydrolyzed Urines Excreted on Low- and High-protein Diets**

(Values given as mg. per 24 hours per 70 Kg. body weight)

AMINO ACID†	LOW-PROTEIN DIET				HIGH-PROTEIN DIET				
	Average of M.D.M. per individual‡	Range§	Mean¶ (A^1)	M.D.M. for (A^1)	Average of M.D.M. per individual‡	Range§	Mean¶ (B^1)	M.D.M. for (B^1)	Increase of (B^1) over (A^1)‖
	per cent			*per cent*	*per cent*			*per cent*	*per cent*
Arginine	8.8	13 to 20	16	15.7	7.1	17 to 24	20	8.0	25
Cystine	4.0	50 to 88	66	9.5	9.7	174 to 332	236	14.6	258**
Glutamic Acid	7.2	21 to 28	24	8.4	6.5	16 to 23	19	11.8	21**
Glycine	6.8	527 to 966	746	13.0	10.2	525 to 1,169	968	16.7	30
Histidine	15.0	44 to 136	91	26.3	5.4	76 to 212	145	17.8	59
Lysine	19.9	13 to 29	21	21.8	26.9	10 to 43	27	40.0	29
Phenylalanine	7.2	5 to 19	11	22.7	7.2	7 to 14	11	16.2	0
Tryptophan	4.5	8 to 22	14	21.6	8.2	13 to 29	20	17.8	43
Tyrosine	16.0	11 to 26	17	30.5	10.4	13 to 27	22	18.4	29
Average	9.9			18.8	10.2			17.9	31

* Summary of data obtained from nine normal males. The weight (lbs.) and the age (years), respectively, of each subject were: 190-26, 185-27, 175-26, 155-26, 155-25, 149-26, 140-29, 135-26, and 135-26. No correlation was noted between the weights or ages of the subjects and their excretions, calculated in mg. per 24 hours per 70 Kg. body weight.

† Values are omitted for some amino acids which could not be determined with satisfactory accuracy. Maximum values found for these amino acids were 10 (aspartic acid), 22 (isoleucine), 29 (leucine), 18 (methionine), 25 (threonine), and 13 (valine).

‡ The per cent mean deviation from the mean was calculated for each individual's average excretion. The values given are the averages of these calculated percentages.

§ Range of average values for nine subjects.

¶ Mean of average values for nine subjects.

‖ Calculated as $[(B^1) - (A^1)] \times 100/(A)$.

** Omitted in calculating the average.

employed in the present experiments was not markedly different or more constant than that found by Woodson *et al.* (7) for 18 subjects (13 males) on usual dietary regimens.

The excretion (unhydrolyzed urines, table 4) of each amino acid by the different individuals deviated from the mean values for 7 amino acids by 18.8 (8.4 to 30.5) per cent on the low-protein diet and by 17.9 (8.0 to 40.0) per cent on the high-protein diet. That these deviations are greater than those found for the corresponding hydrolyzed samples may be explained by differences between the subjects in their metabolism, yielding unlike proportions or types of bound

amino acids. Such dissimilarities would result in different apparent activities (determined before hydrolysis) even though the amounts of amino acids excreted (determined after hydrolysis) were much more constant.

It may be noted that the excretion (unhydrolyzed urines) of amino acids (excluding cystine and glutamic acid) averaged 30 (0 to 59) per cent greater on the high-protein than on the low-protein diet (table 4). Similarly the excretion (hydrolyzed urines) of amino acids (table 5) was 15 (5.0 to 31) per cent greater on the high-protein than on the low-protein diet. It is of interest, also, that the amino acids excreted either on the low-protein or the high-protein diet were

TABLE 5

*Amino Acids in Hydrolyzed Urines Excreted on Low- and High-protein Diets**

(Values given as mg. per 24 hours per 70 Kg. body weight)

AMINO ACID	LOW-PROTEIN DIET				HIGH-PROTEIN DIET				
	Average of M.D.M. per individual‡	Range‖	Mean¶ (A^3)	M.D.M. for (A^3)	Average of M.D.M. per individual‡	Range‖	Mean¶ (B^3)	M.D.M. for (B^3)	Increase of (B^3) over (A^3)‖
	per cent			*per cent*	*per cent*			*per cent*	*per cent*
Arginine	3.3	17 to 23	20	7.9	4.8	19 to 24	21	6.3	5.0
Aspartic Acid	5.9	101 to 126	114	5.3	8.2	103 to 166	135	11.0	18.0
Glutamic Acid	5.8	234 to 369	297	17.4	5.7	251 to 393	320	13.1	7.7
Glycine	7.1	501 to 812	648	12.4	7.8	393 to 921	690	16.4	6.5
Histidine	6.7	82 to 156	124	7.5	4.1	92 to 203	162	14.1	31.0
Isoleucine	3.8	12 to 15	13	3.7	6.7	10 to 20	14	16.5	7.7
Leucine	4.7	18 to 20	19	4.1	3.8	17 to 26	21	12.4	11.0
Lysine	6.1	37 to 49	42	7.9	5.3	43 to 67	51	13.4	21.0
Methionine	4.8	8 to 13	11	12.4	9.4	9 to 15	12	15.4	9.1
Phenylalanine	3.6	14 to 20	16	11.4	4.0	16 to 24	20	11.2	25.0
Threonine	5.0	27 to 51	38	13.6	5.7	35 to 54	45	12.9	18.0
Valine	3.7	22 to 25	23	4.3	9.2	21 to 32	27	19.6	17.0
Average	5.0			9.0	6.2			13.5	15.0

* For Footnotes to table 5, see corresponding footnotes to table 4.

less than 5 per cent of the amino acids ingested as protein in the food (table 3).[7] It may be concluded, therefore, that a large part of the amino acids which are available in excess of the need for protein building and other special functions is utilized by the body for other purposes or is converted to inactive substances before being excreted.

It may be seen that glutamic acid excretion as determined in unhydrolyzed urine was 21 per cent lower on the high-protein diet than on the low-protein

[7] About 10 per cent of ingested DL-methionine is excreted in the urine according to Wheeler and György (15). Methionine excretion was less than one per cent of that supplied by the protein of either diet in the present experiments. This difference seems to support the view that the percentage utilization of an amino acid may depend on the ratio of that amino acid to other amino acids in the diet (16).

diet (table 4). Glutamic acid excretion determined in hydrolyzed urine, however, was 7.7 per cent higher on the high-protein diet than on the low-protein diet (table 5). Similarly, phenylalanine excretion determined in unhydrolyzed urines (table 4) was the same on both diets, but was 25 per cent higher on the high-protein diet as determined in the hydrolyzed urine (table 5). The remaining amino acids (tables 4 and 5) were higher (either hydrolyzed or unhydrolyzed urines) on the high-protein diet than on the low-protein diet. However, the percentage difference in excretion on the high- and low-protein diets was greater for each amino acid (except phenylalanine) determined in the unhydrolyzed urines than in the corresponding hydrolyzed samples. These observations indicate that the proportions and types of excreted amino-acid complexes (in unhydrolyzed urine) may be influenced by diet to a greater extent than the amino acids (in hydrolyzed urine). The fourfold increase in cystine excretion (table 4) by normal subjects on the high-protein diet suggests that dietary control is essential in clinical studies on the excretion of this amino acid.

SUMMARY

A total of 15 amino acids (15 in unhydrolyzed and 12 in hydrolyzed samples) have been determined by microbiological methods in 24-hour urines of 9 normal male subjects maintained in separate experiments on rigidly controlled low-protein and high-protein diets. The excretion of (apparent) amino acids was more nearly constant in successive 24-hour urines of the same and different individuals in the hydrolyzed than in the unhydrolyzed urines. The excretion of amino acids (hydrolyzed urines) was only about 15 per cent greater on the high-protein than on the low-protein diet even though the amino acids determined in the former diet were about 2.4 times those in the latter. The excretion of amino acids (unhydrolyzed urines) averaged about 30 per cent greater on the high-protein than on the low-protein diet except for cystine, which increased about fourfold, and glutamic acid, which decreased about 21 per cent. In general, the amounts of amino acids excreted on the rigidly controlled high-protein diet were not markedly different than those found by earlier workers for subjects maintained on arbitrary dietary regimens. It appears that the amino acid excretion of adult males normally is inconstant although within limits which have been reasonably well defined in the experiments of the present as well as of earlier investigators.

SUMARIO

Excreción Urinaria de Acidos Amínicos en Varones Normales a Dietas Ricas y Pobres en Proteína, Comprobadas

Un total de 15 amino-ácidos (15 en muestras sin hidrolizar y 12 en las hidrolizadas) fué determinado con técnicas microbiológicas en las orinas de 24 horas de 9 varones normales, mantenidos en experimentos independientes a dietas ricas y pobres en proteína, rígidamente comprobadas. La excreción de ácidos amínicos (aparentes) fué más cuasiconstante en las orinas sucesivas de 24 horas de los mismos y de distintos individuos en las muestras hidrolizadas que en las

sin hidrolizar. La excreción amino-ácida (orinas hidrolizadas) fué sólo aproximadamente 15 por ciento mayor con la dieta rica que con la pobre en proteína, aunque los ácidos amínicos determinados con la primera representaron unas 2.4 veces los de la última. La excreción amino-ácida (muestras sin hidrolizar) promedió aproximadamente 30 por ciento más con la dieta rica que con la dieta pobre en proteína, salvo por la cistina, que aumentó casi el cuádruple, y el ácido glutámico, que disminuyó aproximadamente 21 por ciento. En general, las cantidades de ácidos amínicos excretados con la dieta rica en proteína, rígidamente comprobada, no discreparon mayor cosa de las observadas por investigadores anteriores en sujetos mantenidos con régimenes dietéticos arbitrarios. Según parece, la excreción de ácidos aminados de los varones adultos es normalmente inconstante, aunque dentro de ciertos límites bastante bien definidos en estos, así como en anteriores, experimentos.

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THE URINARY EXCRETION OF AMINO ACIDS: II. BY TUBERCULOUS MALE SUBJECTS ON CONTROLLED LOW- AND HIGH-PROTEIN DIETS[1]

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INTRODUCTION

The role that protein nutrition plays in the resistance to tuberculosis is not yet established. It has been found that serum globulin increases abruptly with the onset of the disease (1) and the concentration of albumin drops suddenly in far advanced cases of tuberculosis. The albumin concentration seems to be intimately related to the erythrocyte sedimentation rate (2) which usually becomes increasingly higher as the disease progresses. The object of the work reported in this paper was to discover the differences and similarities of amino acid excretion between two groups on the same protein intake: one group composed of tuberculous subjects, the other of normal individuals. The values obtained for the normal subjects have been reported in the preceding paper in this series (11). The amino acid excretions of the tuberculous patients are tabulated in the present report and comparisons drawn with the results obtained from the normal subjects.

Experimental

The subjects used in this study were all male tuberculous patients with moderately advanced disease who were maintained on strict bed rest at The Charles Cook Hastings Home. The length of time spent in this hospital at the time of the diets ranged between one and eleven months, with an average stay of seven months. None of them had been treated by surgical means or streptomycin. These factors kept outside influences at a minimum, so that any results obtained were, as far as possible, the direct result of the diets consumed.

The diets were exactly the same as those discussed and tabulated in the preceding paper (11). In the first half of the experiment, 10 patients were maintained four days on the low-protein diet, consisting of 49 Gm. of protein per 70 Kg. of body weight daily. The vitamin and mineral levels were adequately maintained[2]; total calories were 2,500 and the fluid intake was restricted to approximately one liter per day. Twenty-four-hour urine samples were collected on the fourth day. The same 10 patients were maintained four days on the high-protein diet consisting of 95 Gm. of protein per 70 Kg. of body weight in the second half of the experiment. Caloric and fluid intake were kept the same as in the preceding experiment. Twenty-four-hour urine samples were collected on

[1] From The Charles Cook Hastings Home, Altadena, California, and the Chemical Laboratory, University of California, Los Angeles, California.

[2] Four of the patients were receiving supplements of vitamins A and C.

the fourth day and all samples were preserved under toluene and refrigerated. The figure of 95 Gm. of protein used in the high-protein diet was arbitrarily chosen because that is the average amount present in the daily diet of patients in this hospital.

The amino acids were determined by the microbiological procedures described in papers (3, 4, and 10). The samples were treated in the same manner as dis-

TABLE 1

*Amino Acids in Unhydrolyzed Urines from Tuberculous Patients on Low- and High-protein Diets**

(Values given as mg. per 24 hours per 70 Kg. body weight)

AMINO ACID†	LOW-PROTEIN DIET			HIGH-PROTEIN DIET			
	Range§	Mean¶ (A^3)	M.D.M. for (A^3)	Range§	Mean¶ (B^3)	M.D.M. for (B^3)	Increase of (B^3) over (A^3)‖
			per cent			*per cent*	*per cent*
Arginine	12 to 23	16	20.6	10 to 23	18	21.1	12.5
Cystine‡	202 to 426	288	16.5	203 to 655	437	13.0	51.7**
Glutamic Acid	14 to 32	22	21.2	12 to 30	18	18.2	−18.3**
Glycine	465 to 850	688	18.3	489 to 1,109	868	16.9	26.2
Histidine	92 to 200	137	19.3	105 to 282	190	22.2	38.7
Lysine	27 to 99	50	29.7	31 to 165	70	45.8	40.0
Phenylalanine	10 to 19	15	18.8	12 to 23	16	12.7	6.7
Tryptophan‡	14 to 30	19	18.3	19 to 31	23	11.3	21.1
Tyrosine‡	18 to 51	31	26.1	23 to 59	38	26.4	22.6
Average			21.0			20.8	24.0

* Summary of data obtained from 10 tuberculous males. The weight (lbs.) and age (years), respectively, of each subject were: 175-24, 159-27, 176-36, 157-20, 178-25, 208-28, 191-38, 177-21, 169-20, 167-26.

† The following amino acids were also determined on all the unhydrolyzed urine samples with the following maximum values: 71 (aspartic acid), 53 (isoleucine), 30 (leucine), 22 (methionine), 38 (threonine), 30 (valine).

‡ Cystine, tryptophan and tyrosine were assayed only on unhydrolyzed samples because of their partial destruction on acid hydrolysis.

§ Range of average values for 10 tuberculous subjects.

¶ Mean of average values for 10 tuberculous subjects.

‖ Calculated as $[(B^3) - (A^3)] \times 100/(A^3)$.

** Omitted in calculating the average.

cussed in the preceding paper. The mean deviations from the mean values for the different levels of samples averaged between 4 and 5 per cent.

RESULTS

In making a comparison of the tuberculous and normal subjects, the following points were noted: The percentage increase of amino acid excretion resulting from the higher protein intake averaged 24.1 per cent[3] (6.7 to 40.0) on the unhydrolyzed samples of the tuberculous patients (table 1). The percentage in-

[3] Cystine and glutamic acid percentages excluded.

crease for the normal subjects under the same circumstances averaged 30.0[3] (0.0 to 59.0, table 4, preceding paper (11)). On the hydrolyzed samples, the tuberculous subjects averaged 3.1 per cent (−13.5 to 19.4, table 2), while the normal subjects averaged a 15.0 per cent (5.0 to 31.0, table 5, preceding paper (11)) increase in amino acid output over the low protein diet.

It was found that the glutamic acid excretion of the tuberculous subjects was similar to that of the normal subjects in that, although there was a decrease in the per cent excretion on the high-protein diet (−18.3, unhydrolyzed

TABLE 2

*Amino Acids in Hydrolyzed Urines from Tuberculous Patients on Low- and High-protein Diets**

(Values given as mg. per 24 hours per 70 Kg. body weight)

AMINO ACID	LOW-PROTEIN DIET			HIGH-PROTEIN DIET			
	Range†	Mean‡ (A^4)	M.D.M. for (A^4)	Range†	Mean‡ (B^4)	M.D.M. for (B^4)	Increase of (B^4) over (A^4)§
			per cent			*per cent*	*per cent*
Arginine	20 to 33	26	9.0	24 to 31	26	5.7	0.0
Aspartic Acid	64 to 175	124	15.0	121 to 157	138	6.6	11.3
Glutamic Acid	209 to 514	328	19.2	229 to 401	341	10.2	4.0
Glycine	491 to 780	635	11.2	335 to 703	549	19.0	−13.5
Histidine	120 to 204	160	14.0	122 to 288	191	15.4	19.4
Isoleucine	11 to 20	14	14.0	14 to 17	15	7.2	7.1
Leucine	17 to 32	21	14.6	14 to 23	19	12.0	−9.5
Lysine	42 to 117	62	21.5	41 to 127	69	26.7	11.3
Methionine	8 to 14	11	19.2	8 to 14	11	17.7	0.0
Phenylalanine	11 to 33	22	19.0	20 to 29	23	8.9	4.5
Threonine	34 to 61	46	15.3	36 to 65	49	16.5	6.5
Valine	17 to 32	22	15.0	16 to 25	21	8.4	−4.5
Average			15.6			12.9	3.1

* See Note 1 for table 1.

† Range of average values for 10 tuberculous subjects.

‡ Mean of average values for 10 tuberculous subjects.

§ Calculated as $[(B^4) - (A^4)] \times 100/(A^4)$.

samples), this was reversed and the glutamic acid excretion was increased by 4.0 per cent on the high-protein diet when the samples were hydrolyzed. Cystine had the highest percentage increase of any of the amino acids with 51.7 per cent over the low-protein diet excretion. This was much lower, however, than the normal subjects, whose cystine excretion on the high-protein diet was 258 per cent higher. Since the cystine output was so much higher on the low-protein diet of the tuberculous patients (288 mg. per 24 hours per 70 Kg.) than that of the normal subjects (66 mg. per 24 hours per 70 Kg.), it would seem to indicate that the tuberculous patients do not retain this sulfur-containing amino acid as well as the normal subjects, or that they have a greater need for

it, possibly because of its combination and subsequent excretion as a detoxifying agent.

In table 3 is shown the percentage change between the tuberculous and normal subjects. On the low-protein diet, using the unhydrolyzed samples, cystine was found to be increased fourfold by the tuberculous subjects (336 per cent). When the high-protein diet was used, the percentage increase was not quite

TABLE 3

Differences in Amino Acid Excretion of Tuberculous and Normal Subjects on Low- and High-protein Diets

(Values given as mg. per 24 hours per 70 Kg. body weight)

AMINO ACID	UNHYDROLYZED URINES				INCREASE OF TB. OVER NORM. SUBJECTS		HYDROLYZED URINES				INCREASE OF TB. OVER NORM. SUBJECTS	
	Norm. Subj.		TB. Subj.				Norm. Subj.		TB. Subj.			
	Low A^1 Mean	High B^1 Mean	Low A^3 Mean	High B^3 Mean	Low* per cent	High† per cent	Low A^2 Mean	High B^2 Mean	Low A^4 Mean	High B^4 Mean	Low‡ per cent	High§ per cent
Arginine	16	20	16	18	0.0	−10.0	20	21	26	26	30.0	23.8
Aspartic Acid	—	—	—	—	—	—	114	135	124	138	8.8	2.2
Cystine	66	236	288	437	336.4¶	85.2¶	—	—	—	—	—	—
Glutamic Acid	24	19	22	18	−8.3	−5.3	297	320	328	341	10.4	6.6
Glycine	746	968	688	868	−7.8	−10.3	648	690	635	549	−2.0	−20.4
Histidine	91	145	137	190	50.5	31.0	124	162	160	191	29.0	17.9
Isoleucine	—	—	—	—	—	—	13	14	14	15	7.7	7.1
Leucine	—	—	—	—	—	—	19	21	21	19	10.5	−9.5
Lysine	21	27	50	70	138.1	159.3	42	51	62	69	47.6	35.3
Methionine	—	—	—	—	—	—	11	12	11	11	0.0	−8.3
Phenylalanine	11	11	15	16	36.4	45.5	16	20	22	23	37.5	15.0
Threonine	—	—	—	—	—	—	38	45	46	49	21.1	8.9
Tryptophan	14	20	19	23	35.7	15.0	—	—	—	—	—	—
Tyrosine	17	22	31	38	82.4	72.7	—	—	—	—	—	—
Valine	—	—	—	—	—	—	23	27	22	21	−4.3	−22.2
Average					40.9	37.2					16.4	4.7

* Calculated as $[(A^3) - (A^1)] \times 100/(A^1)$.
† Calculated as $[(B^3) - (B^1)] \times 100/(B^1)$.
‡ Calculated as $[(A^4) - (A^2)] \times 100/(A^2)$.
§ Calculated as $[(B^4) - (B^2)] \times 100/(B^2)$.
¶ Omitted in calculating the average.

twofold (85.2 per cent). The values for lysine showed the next highest percentage increase of tuberculous over normal subjects with 138 per cent on the low-protein diet and 159 per cent on the high-protein diet. This was reduced to 47.6 and 35.3 per cent, respectively, however, when the hydrolyzed samples were examined.

Although the values for cystine deviated the most strikingly from the normal, it is noteworthy that, on the whole, the excretion of most of the amino acids was increased on both diets by the tuberculous subjects when the unhydrolyzed sam-

ples were assayed with an average increase of 40.9 on the low-protein and 37.2 per cent on the high-protein diet. Glutamic acid and glycine were the only exceptions[4] with slight decreases for both of them. The amounts of glutamic acid found in the hydrolyzed samples reversed this trend, but glycine was still slightly decreased in amount.

The average percentage increase of the amino acids excreted by the tuberculous patients over the nontuberculous subjects was lowered when the hydrolyzed samples were assayed. On the low-protein diet, the average percentage increase was 16.4 while on the higher amount it was only 4.7 per cent. The fact that the average amino acid excretion of the tuberculous over the normal subjects was persistent, although small, would seem to indicate some difference in metabolism between the two groups. The larger difference when the unhydrolyzed samples were used might be explained, as in the preceding paper (11), where the possibility that there was a difference in the amount of bound amino acids was set forth. This difference was lowered when the hydrolyzed samples were used and the average 4.7 per cent increase of the tuberculous over the normal subjects on the high-protein diet is insignificant. It is also noteworthy that, when the amounts of the amino acids excreted by the normal and tuberculous subjects were compared, the tuberculous subjects excreted proportionately larger amounts of amino acids on the low-protein diet than they did on the high-protein diet.

In drawing a parallel between the two groups of subjects, it might be said that there were relatively greater differences in amino acid excretion on a group basis than on the amount of protein ingested. Woodson *et al.* (5) also reported no significant variations in amino acid excretion, although their subjects were on a wide variety of "normal" diets. The same observation was made by Yeh *et al.* (6), who assayed the amino acid excretion of 7 normal females, and found a remarkably uniform pattern in spite of dietary and age differences.

Cystinuria was the most marked deviation found in the tuberculous subjects. The cystine levels attained by these patients were as high as those found by several workers investigating the cystine excretion of cystinurics. Bodansky and Bodansky (7) reported levels between 400 and 1,000 mg. for cystinuric subjects while Yeh *et al.* found an average excretion of 291 mg. per twenty-four hours on one patient who was tested on seven consecutive days. In trying to find a correlation between cystine excretion and the relative toxicity of the individual tuberculous infections no conclusions could be drawn.

Since cystine is one of the end products of the metabolism of methionine, the problem may be one involving this amino acid rather than of cystine alone. Brand and co-workers (8 and 9) found that the cystinuric individual was capable of using almost completely large amounts of cystine fed as the free amino acid. On the contrary, methionine or cystine, when fed, increased the output of cystine. In an attempt to establish whether the large amount of cystine present in the urine of tuberculous patients was due to detoxification with cystine or due to incomplete metabolism of amino acid sulfur, it was decided to assay the

[4] Glycine values decreased 8.3 per cent on low-protein and 5.3 per cent on high-protein; glutamic acid values decreased 7.8 per cent on low-protein and 10.3 on high-protein diet.

twenty-four-hour samples from tuberculous subjects for inorganic sulfates, ethereal sulfates, and neutral sulfur before and after giving them extra methionine. The results from this work will be reported at a later date.

SUMMARY

1. Microbiological assays were performed on 24-hour urine specimens from 10 male subjects with moderately advanced tuberculosis for fifteen amino acids (15 on unhydrolyzed and 12 on hydrolyzed samples).

2. The results were compared with those obtained on 9 normal male subjects reported in the preceding paper (11), and the following points were noted:

(a) The normal patients had an average increase of 30.0 per cent in amino acid excretion due to the high protein diet as compared to a 24.1 per cent increase by the tuberculous subjects (unhydrolyzed samples).

(b) On the hydrolyzed samples, the normal subjects increased their amino acid excretion as a result of the high protein diet by 15.0 per cent as compared to 3.1 per cent by the tuberculous.

(c) The highest percentage increase (51.7) of any of the amino acids resulting from diet alone was observed for cystine.

(d) The average cystine output of the tuberculous subjects on the low-protein diet was 288 mg. per 24 hours per 70 Kg. of body weight, as compared to 66 mg. by the normal subjects. On the high-protein diet, the tuberculous subjects excreted 437 mg. as compared to 236 by the normals. This was found to be a fourfold increase over the normal subjects on the low-protein diet (336 per cent) and almost twofold increase on the high protein diet (85.2 per cent).

(e) Some difference in the metabolism of the other amino acids between the two groups was suggested by the small but persistent average increase in amino acid excretion by the tuberculous subjects.

SUMARIO

Excreción Urinaria de Acidos Amínicos por Varones Tuberculosos con Dietas Ricas y Pobres en Proteína

1. En ejemplares de orina de 24 horas, procedentes de 10 sujetos varones con tuberculosis moderadamente avanzada, ejecutáronse valoraciones microbiológicas en busca de 15 amino-ácidos (15 en muestras sin hidrolizar y 12 en las hidrolizadas).

2. Al comparar el resultado con el obtenido en 9 varones normales, y descrito en el trabajo anterior, notáronse los siguientes puntos:

(a) Los sujetos normales mostraron un aumento medio de 30.0 por ciento en la excreción de amino-ácidos, debido a la dieta rica en proteína, comparado con 24.1 por ciento en los tuberculosos (muestras sin hidrolizar).

(b) En las muestras hidrolizadas, los sujetos normales aumentaron, por virtud de la dieta rica en proteína, su excreción de ácidos amínicos en 15.0 por ciento, comparado con 3.1 por ciento en los tuberculosos.

(c) De todos los amino-ácidos, la cistina fué el que mostró mayor aumento porcentario (51.7), por virtud de la dieta solamente.

(d) La excreción media de cistina por los tuberculosos con el régimen pobre en proteína fué de 288 mg. en 24 horas por 70 kg. de peso del individuo, comparado con 66 mg. en los sujetos normales. Con el régimen rico en proteína, los tuberculosos excretaron 437 mg., comparado con 236 en los normales. El aumento en los tuberculosos, comparados con los sujetos normales, fué, pues, cuádruple con el régimen bajo en proteína (336 por ciento) y casi doble (85.2 por ciento) con el rico en proteína.

(e) El pequeño, pero persistente, aumento medio en la excreción amino-ácida por los tuberculosos indica alguna diferencia en el metabolismo de los otros ácidos amínicos por los dos grupos.

Acknowledgment

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STUDIES OF FOOD INTAKE AND REQUIREMENTS OF WOMEN WITH ACTIVE AND ARRESTED TUBERCULOSIS[1,2]

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INTRODUCTION

As a part of a long time study of the role of nutrition in adult vitality and early senescence, the food patterns of active women from 18 to 80 years of age have been sampled by workers in this laboratory. The dietary practices of these women have been described previously (1). For successive age groups, the mean caloric intakes were as follows: 17 to 25 years, 2,177 calories; 20 to 29 years, 2,180 calories; 25 to 35 years, 1,953 calories; and 40 to 69 years, 1,658 calories. Thus women in the North Central region are accustomed to food patterns with a quantity of food supplying 1,700 to 2,200 calories per day. This caloric intake was necessary to provide 60 Gm. of protein daily on self-selected diets. Among women over forty years of age, there was some evidence that chronic ill health accompanied dietary inadequacies, particularly calories and protein.

The question of suitable dietary recommendations for women with active and arrested tuberculosis was presented to this laboratory in a request for recommendations for food subsidies for patients discharged from sanatoriums. Although there has been recognition of the difficult feeding problem associated with the tuberculous patient (2), there is little information in the literature concerning the intake and utilization of food by individuals with tuberculosis. Recommendations of 3,000 calories or more per day (3) exceed the amounts of food which moderately active, healthy women eat. Since the diet must be planned in terms of quantities of food which the patient can and will consume, the food intake patterns of women with active and arrested tuberculosis have been studied. The techniques of dietary survey were comparable to those used in similar studies with healthy women so that comparison may be made among the three groups. Information also was obtained concerning the utilization of nitrogen and ascorbic acid by some of the subjects of this study.

PLAN OF INVESTIGATION

A survey of food habits was conducted at the Ingham County sanatorium in Michigan, with women from ages of 18 to 45. There were two groups of subjects; one included 30 nonambulatory patients with minimal or moderately advanced active tuberculosis; the second group was made up of 35 women with arrested tuberculosis who were former patients of the sanatorium and who attended the outpatient clinic at regular intervals. Eleven of the women with arrested tuber-

[1] From the Foods and Nutrition Department, Michigan State College, East Lansing, and Ingham County Sanatorium, Lansing, Michigan.

[2] Authorized for publication as Journal article No. 1005 (n.s.) of the Michigan Agricultural Experiment Station.

culosis had been readmission cases at the sanatorium and the interval since the last discharge varied from one month to nine years.

Through personal interviews, information was obtained about the economic status and food habits and a series of seven daily food records was collected from each subject. The nutritive value of the diets was calculated by the procedure of Donelson and Leichsenring (4) and these values were compared with data for apparently healthy women as reported by Greenwood (5).

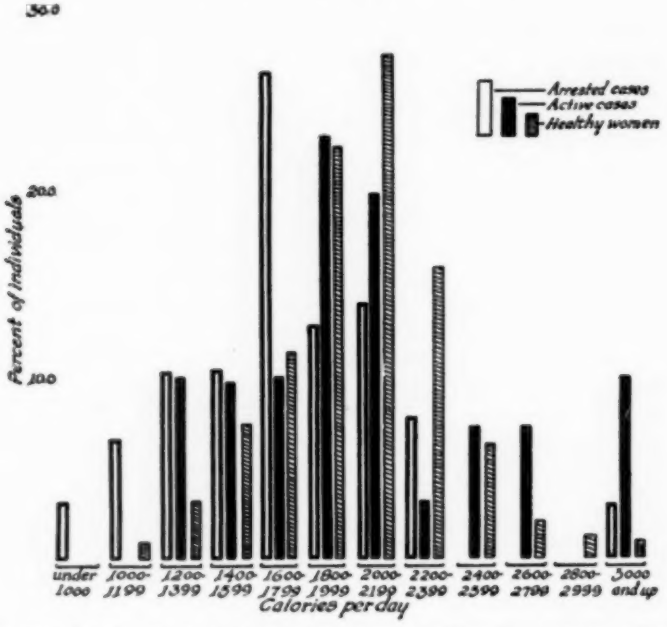

FIG. 1. Distribution of calories in the diets of women with active and arrested tuberculosis, and of healthy women.

RESULTS

The caloric intakes for the three groups are given in figure 1. The daily caloric intakes for healthy women exceeded those for tuberculous women. For the healthy women, the peak of distribution occurred at an intake of 2,000 to 2,199 calories, whereas for women with active tuberculosis the peak of distribution was at an intake of 1,800 to 1,999 calories, and at an intake of 1,600 to 1,799 calories for women with arrested tuberculosis. Sixty per cent of the patients with arrested tuberculosis had daily caloric intakes of less than 1,800 calories; for twenty per cent of the group, the intakes averaged less than 1,400 calories per day.

The intake of food by women with arrested tuberculosis did not vary quantitatively with the degree of physical activity. The factors which did appear to be responsible for the limited food intake were fatigue, lack of adequate finances for household help as well as for food, and lack of appetite. For the patients with active tuberculosis, the factors which were apparently important in limiting food intake were lack of appetite and the desire to control weight.

The protein content of the diets is given in table 1. The proportion of tuberculous women with intakes of protein above 75 Gm. was higher than for healthy women. However, 33 per cent of women with arrested tuberculosis and 38 per cent of women with active tuberculosis had protein intakes less than 62.5 Gm. There was a positive relationship between the protein and caloric contents of the diet. For women with arrested tuberculosis, the correlation coefficient was 0.802 and this was statistically significant.

TABLE 1

The Protein Intake of Healthy College Women and Women with Active and Arrested Tuberculosis

PROTEIN INTAKE PER DAY	HEALTHY COLLEGE WOMEN	WOMEN WITH TUBERCULOSIS	
		Active	Arrested
	per cent	*per cent*	*per cent*
Below 50.0 Gm.	8	10	8
50.0 to 62.4 Gm.	31	28	25
62.5 to 74.9 Gm.	46	24	31
75.0 to 87.4 Gm.	14	17	28
87.5 Gm. and above	1	21	8

A comparison of the distribution and occurrence of certain classes of foods in the diets of tuberculous and healthy women is shown in table 2. The patterns of food consumption for the three groups were similar. Twenty-two per cent of the women with arrested tuberculosis had less than one cup of milk daily, whereas 13 per cent had an intake of three or more cups per day. Thirty per cent of the arrested cases averaged less than one serving of meat daily and there was less than one serving of citrus fruit daily in the diets of 52 per cent of the women with arrested tuberculosis.

Since the patterns of food selection by tuberculous women were similar to those for healthy women, it appeared probable that a restricted intake of essential nutrients would parallel the limited caloric intakes. Evidence for this in respect to the diets of women with arrested tuberculosis is shown in table 3. The intakes of various nutrients were less than the amounts recommended by the Food and Nutrition Board of the National Research Council (6) for 76 per cent of the women in the case of iron and thiamine, 64 per cent in the case of vitamin A, and 45 per cent in respect to ascorbic acid. The calcium and riboflavin intakes were closely related to the protein intake; milk was the important source of these nutrients in the diets. Limited usage of cereals and meat restricted the intakes of thiamine and iron.

The analyses of dietaries of women with active tuberculosis represented the selection of food from the diet tray by the individual and were not an evaluation of the adequacy of the hospital diet as it was served. The upper range of values given in the preceding tables probably indicates the quantity of nutrients offered in the sanatorium diet. The differences in intakes for patients eating from the same hospital diet demonstrate an important problem in feeding in tuberculosis, *i.e.*, that the patient must be encouraged and educated to eat quantitatively the

TABLE 2

Percentage Distribution of Tuberculous and Healthy Women According to Occurrence of Certain Foods in Diet

FOOD GROUP	NUMBER OF TIMES EATEN PER WEEK					
	0	1 to 3	4 to 6	7 to 13	14 to 20	21 or more
	per cent	*per cent*	*per cent*	*per cent*	*per cent*	*per cent*
Milk						
Women, arrested tuberculosis	3	3	16	32	32	13
Women, active tuberculosis			10	14	52	24
Women, healthy	3	10	16	39	29	3
Green and Yellow Vegetables						
Women, arrested tuberculosis			26	68	3	3
Women, active tuberculosis		3	24	66	7	
Women, healthy	1	9	31	54	5	
Citrus Fruits						
Women, arrested tuberculosis	6	23	23	48		
Women, active tuberculosis		14	17	59	10	
Women, healthy	2	18	37	41	2	
Meat						
Women, arrested tuberculosis			30	61	6	3
Women, active tuberculosis		3	3	62	32	
Women, healthy		2	12	82	5	

food that is provided for him. If good dietary habits are developed during the sanatorium stay, these habits may continue after the disease is arrested.

The food intake patterns for tuberculous women which have been presented reflect the dietary habits of the group. Metabolic data also are necessary, however, for evaluation of the quantitative nutritional requirements. Data were obtained concerning the utilization of nitrogen and of ascorbic acid by women from the group studied in the survey.

Nitrogen retentions of tuberculous women: Six women with moderately advanced, active, afebrile tuberculosis whose sputum contained tubercle bacilli were subjects for nitrogen balance studies for a period of fifteen weeks. There were five,

seven-day balance periods, each preceded by a period of fourteen days for dietary adjustment. The protein content of the usual hospital diet was varied by adjustment of the milk intake of the different periods. Weighed food consumption

TABLE 3

The Calcium, Iron, Protein, and Vitamin Content of Diets of 33 Women with Arrested Tuberculosis*

NUTRIENT	NUMBER INDIVIDUALS
Calcium	
0.8 Gm. and above	19
0.5 to 0.79 Gm.	8
Less than 0.5 Gm.	6
Riboflavin	
1.5 mg. and above	21
1.0 to 1.49 mg.	7
Less than 1.0 mg.	5
Protein	
60 Gm. and above	23
50 to 59 Gm.	7
Less than 50 Gm.	3
Iron	
12 mg. and above	7
9 to 11.9 mg.	17
Less than 9 mg.	9
Thiamine	
1.1 mg. and above	8
0.8 to 1.09 mg.	15
Less than 0.8 mg.	10
Ascorbic Acid	
70 mg. and above	18
45 to 69 mg.	8
Less than 45 mg.	7
Vitamin A	
5,000 I.U. and above	12
3,500 to 4,999 I.U.	8
Less than 3,500 I.U.	13

* Determined by calculation

records were obtained for both the adjustment and balance periods. During the balance period, weighed samples of food representing an aliquot portion of the amount eaten and all fecal and urinary excretions were collected. These were prepared for analysis according to the procedure of Stearns (7), and nitrogen was determined by the Kjeldahl method (8). The nitrogen content of beverages and

medicine were analyzed and these values included in the total nitrogen intakes. Preliminary analyses of the nitrogen content of sputum indicated that there was no appreciable excretion by this path; therefore collections of sputum were not made.

The mean nitrogen retentions at various protein intakes are given in table 4. Thirty balances are reported. Data for healthy college women are also included. There were wide individual variations among the data for the tuberculous cases

TABLE 4

The Nitrogen Retentions of Healthy Women and Women with Active and Arrested Tuberculosis; Averages for Seven-day Balance Periods

GROUP	NUMBER OF BALANCES	NITROGEN INTAKE		MEAN PROTEIN* INTAKE	MEAN NITROGEN RETENTION	NUMBER IN NEGATIVE BALANCE
		Range	Mean			
		Gm./24 hrs.	*Gm./24 hrs.*	*Gm./24 hrs.*	*Gm./24 hrs.*	
I Women with active tuberculosis	2	6.00 to 7.99	7.06 ± 0.51†	44.12	−0.02 ± 1.14†	1
	13	8.00 to 9.99	9.18 ± 0.36	57.38	0.73 ± 0.61	3
	3	10.00 to 11.99	10.61 ± 0.47	66.31	1.64 ± 0.24	0
	8	12.00 to 13.99	12.80 ± 0.31	80.00	1.47 ± 0.72	0
	4	14.00 to 15.99	14.78 ± 0.38	92.38	2.16 ± 0.52	0
II Women with arrested tuberculosis	3	7.00 to 9.99	8.72 ± 0.72	54.5	0.72 ± 0.60	1
III Healthy Women	14	6.00 to 7.99	7.11 ± 0.46	44.44	−0.11 ± 0.72	7
	10	8.00 to 9.99	8.93 ± 0.48	55.81	0.28 ± 0.77	4
(a) Cederquist (11)	4	10.00 to 11.99	10.97 ± 0.88	68.56	1.06 ± 0.55	0
	2	12.00 to 13.99	13.74 ± 0.23	85.88	2.13 ± 0.20	0
	1	14.00 to 15.99	15.68 ± 0.00	98.00	1.56 ± 0.00	0
(b) McKay‡ (12)	17	6.00 to 7.99	7.37	46.06	−0.64	14
	45	8.00 to 9.99	9.09	56.81	0.23	15
	41	10.00 to 11.99	10.82	67.62	1.08	5
	14	12.00 to 13.99	12.60	78.75	1.40	0
	6	14.00 to 17.58	15.46	96.62	2.74	0

* Protein = Nitrogen x 6.25

† Mean deviation

‡ Class intervals combined by calculation

as shown by the mean deviations; however, the mean retentions at different intakes closely paralleled the mean retentions for healthy women. There were four individuals in the tuberculous series with negative nitrogen balance at intakes of 62.5 Gm. or less per day. The others in this series were either at equilibrium, or storing nitrogen above this intake. The retention of nitrogen was increased with intake.

From these data, it would appear that the intake of protein necessary for equilibrium is little or no higher for the tuberculous women than for the healthy

individual. For the tuberculous individual, however, an intake of protein adequate for positive nitrogen balance is desirable. An intake of 80 Gm. of protein would appear to be adequate to permit tissue repair for women with a degree of tuberculous infection similar to these patients. A recommended intake of 80 Gm. is practical in terms of cost, diet planning, and appetite limitations.

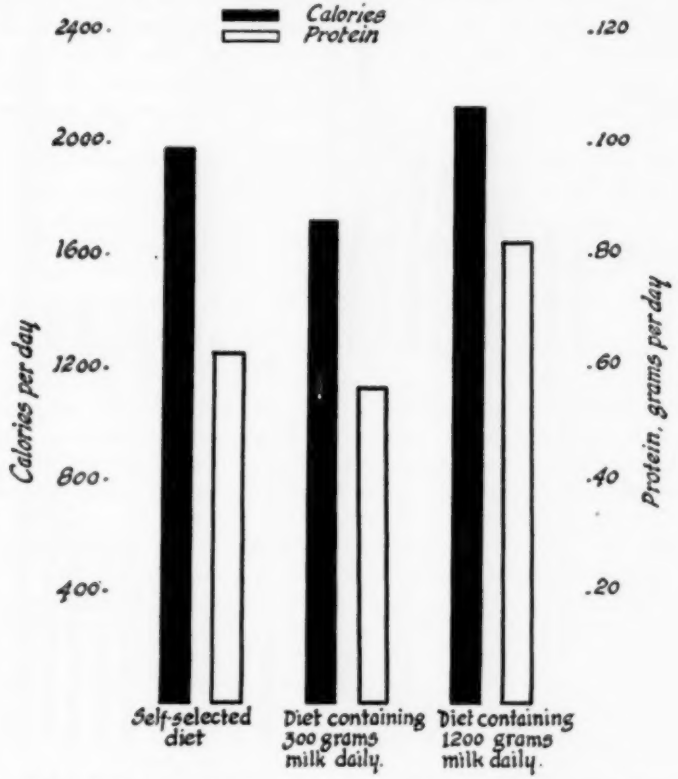

FIG. 2. The caloric and protein content of diets of tuberculous women with variation in milk intake.

When the milk intake was quantitatively increased from 300 Gm. of milk daily to 1,200 Gm. for the subjects on the nitrogen balance study, the average caloric intake was increased by 400 calories per day. This is shown in figure 2. Although to some extent the patient limited intakes of other foods because of additional milk in the diet, the effect of the increased milk was increased calories and increased intakes of protein and calcium. The average weights of the patients were constant on the restricted milk intake and there was an average gain of 2.6 pounds after six weeks on a daily intake of 1,200 Gm. of milk.

The urinary excretion of ascorbic acid by tuberculous and healthy women: Lowered values for ascorbic acid in the plasma and the urine have been reported for tuberculous patients as compared with healthy individuals (9, 10). Little attention has been directed, however, toward the ascorbic acid nutrition of patients with

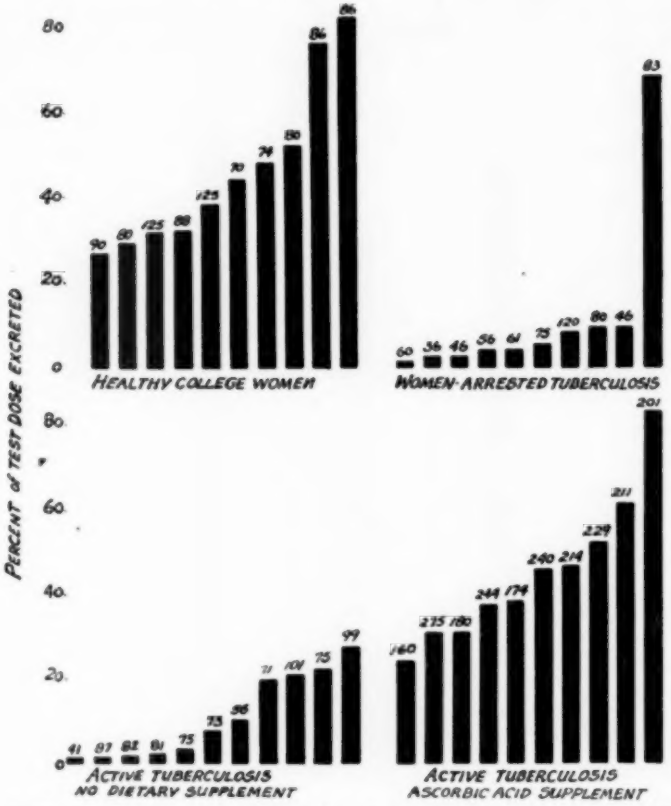

FIG. 3. The per cent excretions of a test dose of ascorbic acid by tuberculous and healthy women.

arrested tuberculosis. In this study the urinary excretion of ascorbic acid following a test dose of 400 mg. was used as a technique for studying the utilization of ascorbic acid by tuberculous women. Twenty-four-hour urine collections were made on three successive days. Reduced ascorbic acid was determined daily by the 2,6 dichlorophenolindophenol method, using a Coleman spectrophotometer. On the fourth day a test dose of 400 mg. of ascorbic acid was given orally and the ascorbic acid of the following 24-hour urine collection was measured. The per cent of the test dose excreted was calculated from the difference between the

excretion before and after the test dose. Data were obtained for women with arrested tuberculosis and bed patients with active tuberculosis. One group of patients with active tuberculosis had received ascorbic acid as a dietary supplement in amounts of 100 mg. or more each day for several months preceding the collections. Another group of patients with active tuberculosis had not had ascorbic acid other than that provided by the daily diet. In addition, data were obtained for senior and graduate women who were free from apparent signs of disease and whose chest roentgenograms revealed no evidence of tuberculosis. The results are shown by the bar diagram in figure 3. The intake of ascorbic acid was calculated and the value for each individual is given above the corresponding bar.

The intake of ascorbic acid for the healthy women was from 70 to 125 mg. and was supplied entirely by the diet. From 26 to 81 per cent of the test dose was excreted in the urine by this group. The per cent excretions of ascorbic acid by women with active tuberculosis were low where the diet was not supplemented. For the group which had received ascorbic acid supplements, however, the excretions were similar to the excretions of healthy college women on a self-selected, unsupplemented diet.

The intake of ascorbic acid for women with arrested tuberculosis varied from 36 to 120 mg. per day. Six of the women had intakes below the amount recommended by the Food and Nutrition Board of the National Research Council (9). The intakes of the others were similar to those for healthy women. The per cent excretions of the test dose for women with arrested tuberculosis were low. Only one individual had a per cent excretion within range of the healthy women. She was a laboratory technician at the hospital, was active socially, and had apparently made a good recovery from the disease.

The low values for the other arrested cases indicate that these women were receiving an inadequate amount of ascorbic acid. The pattern of excretion did not differ greatly from the pattern for women with active tuberculosis on an unsupplemented diet. The number of total values is small for a survey measurement such as the per cent excretion of a test dose. The results indicate, however, that the disturbed metabolism of ascorbic acid in tuberculosis may continue after arrest of the disease and that the ascorbic acid requirement may exceed that of healthy women.

The findings reported here indicate that the recommendations for feeding women patients with tuberculosis need to be directed toward consideration of the disease as one which requires a long time for the healing process to be accomplished. As a consequence, it is necessary for the patient to develop food habits which will allow quantitative intake of nutrients for the rest of her life. With the exception of ascorbic acid, the evidence of increased food requirements in tuberculosis is not as striking as the evidence for the necessity to encourage the tuberculous patient to eat the kind and amounts of food required by normal women. Dietary recommendations providing for an intake of 2,000 to 2,200 calories with 80 Gm. of protein daily appear to be sound from the standpoint of recovery from tuberculosis and also from the standpoint of food habits which the subject may

be expected to continue for a prolonged period. The lowered total intake of food by women with arrested tuberculosis also indicates that a unit of nutrition education should be a part of the rehabilitation program for this group.

SUMMARY

A survey was made of the food habits of 30 women with active tuberculosis and 35 women with arrested tuberculosis and comparisons have been made with food intakes of healthy women. The caloric intakes for women with active tuberculosis varied from 1,300 to 3,000 calories per day. The average caloric intake for the women with arrested disease was about 300 calories per day less than for healthy women or women with active tuberculosis, although the patterns of food selection were similar. The lowered intake of calories by women with arrested tuberculosis was paralleled by a restricted intake of other nutrients.

Nitrogen retentions were studied for 6 women with active, afebrile tuberculosis. There were five seven-day balance periods for each subject and the protein content of the diets was varied by adjustment of the milk intake. Mean daily nitrogen balances are reported.

The daily urinary excretions of ascorbic acid preceding and following a test dose of 400 mg. ascorbic acid were determined for 10 healthy women, 10 women with arrested tuberculosis, and 10 women with active tuberculosis. The ascorbic acid content of the urine was low for both active and arrested cases on their customary diets and after the test dose. However, ascorbic acid excretions for patients with active tuberculosis who had received dietary supplements of 100 to 300 mg. of ascorbic acid per day for at least two months were similar to those for healthy women.

SUMARIO

Estudios de la Ingestión y Requisitos Alimenticios de las Mujeres con Tuberculosis Activa y Estacionada

Tras una encuesta de los hábitos alimenticios de 30 mujeres con tuberculosis activa y 35 mujeres con tuberculosis estacionada, hiciéronse comparaciones con la ingestión alimenticia de mujeres sanas. En lo tocante a calorías, la ingestión de las mujeres con tuberculosis activa varió de 1,300 a 3,000 al día. Para las que tenían la enfermedad estacionada, la ingestión media fué de unas 300 calorías menos, aunque la selección de alimentos se conformó a un patrón semejante. La ingestión menor de calorias por las mujeres con tuberculosis estacionada se reflejó igualmente en la limitada ingestión de otros elementos nutrientes.

Estudióse la retención de nitrógeno en 6 mujeres con tuberculosis afebril, activa, con cinco períodos equilibrados se siete días para cada sujeto, y variándose el contenido de proteína en la dieta por medio del ajuste de la ingestión de leche. Preséntanse las cifras diarias medias de nitrógeno.

La excreción urinaria diaria de ácido ascórbico antes y después de una dosis de ensayo de 400 mg. de dicho ácido fué determinada en 10 mujeres sanas, 10 con tuberculosis estacionada y 10 con tuberculosis activa. El contenido urinario

de ácido ascórbico fué bajo en los casos tanto activos cuanto estacionados con la dieta de costumbre y después de la dosis de ensayo. Sin embargo, la excreción del ácido en las enfermeras con tuberculosis activa que habían recibido complementos dietéticos de 100 a 300 mg. diarios de ácido ascórbico por lo menos durante dos meses fué semejante a la observada en mujeres sanas.

Acknowledgments

Grateful acknowledgment is made to the patients who cooperated with us in this study, to Miss Olive Henderson, dietitian, and to the staff of nurses at the Ingham County Sanatorium. Technical assistance was provided by the following individuals: Betty Brakke, Betty Coles, Dorothy Dunsing, Janet Traver, Helen Tobey, and Violet Katainen.

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AN APPRAISAL OF THE CONTRIBUTION OF MASS RADIOGRAPHY IN THE DISCOVERY OF PULMONARY TUBERCULOSIS[1,2]

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INTRODUCTION

It is proposed in this paper to evaluate the usefulness and the limitations of mass roentgenographic surveys of apparently healthy groups of the population as an instrument of attack upon the prevalence of tuberculosis in a community, such as the city of Baltimore. Through an analysis of a part of the Baltimore City experience with mass chest radiography, the objective of this study is to ascertain to what extent the procedure has demonstrated pulmonary tuberculosis and revealed significant epidemiological differences in the prevalence of tuberculosis in the various groups; to determine what mass radiography has contributed to the discovery of *new* cases of the disease and prompt provision for their medical care and isolation; and to consider its contribution to discovery of cases in the *minimal* stage of the disease in relation to all other means of case notification and discovery available to the health department. This study does not contemplate an assessment of the educational value of such surveys, nor is it concerned with the cost of this method of case finding in comparison with others.

It has long been recognized that the keynote to effective reduction in the prevalence of tuberculosis in any community is early discovery, isolation, and treatment of individuals suffering from active or potentially active pulmonary disease. Under the conditions of medical practice and public health administration which have obtained up to recent years even in the most advanced communities of the United States, progress has been slow in the attainment of this objective. In New York State, for example, Mikol and Plunkett (1) found that, in spite of all efforts to promote earlier diagnosis, the proportion of cases reported in the minimal stage remained at about 20 per cent from 1924 to 1940, and the majority of cases were in the moderately too far advanced stage or dead at the time they came to official attention. With the development of practical and comparatively inexpensive techniques of miniature photography of the chest image on the fluorescent screen (2), a method became available which gave promise of greatly improving this situation. It became possible to examine cheaply, rapidly, and easily large groups of supposedly healthy persons and to discover among them those who were suffering from disease in its minimal stage.

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[2] This report is based on a thesis submitted to the School of Hygiene and Public Health of The Johns Hopkins University in conformity with the requirements for the degree of Doctor of Public Health.

During the past decade, the potentialities of "mass radiography" of the chest of supposedly healthy persons have been explored extensively in this country and abroad and many claims have been put forward regarding the value of this procedure. It has been stated that it not only increases the proportion of cases of tuberculosis which are discovered in the minimal stage of the disease (3), but that it affords an index of measurement of the prevalence of tuberculosis in the community as a whole (4) and points out those groups of the population which are epidemiologically important (5). In addition, by means of periodic re-examinations, it affords an index of incidence (6).

Without attempting to review these reports in detail, it suffices to point out that it is difficult to compare one with another and to judge to what extent these claims have been established. There are many confusing variables. They relate to the manner in which the groups are selected for mass radiography and the extent of participation of the group members (7); the extent to which reading of small films are supplemented by large films (8); the skill and consistency of the film reader (9); the extent to which interpretation of the roentgenogram is supplemented by follow-up clinical and laboratory investigations (10); and, finally, to the criteria used in defining and classifying "cases" of tuberculosis upon which rates and estimates are based (11, 12). While mass radiography of the chest undoubtedly has its place in the epidemiologic attack upon tuberculosis, the values and limitations of this procedure have not yet been clearly delineated.

Baltimore has faced a grave tuberculosis problem for many years. In spite of the fact that mortality from tuberculosis has declined steadily in this city during the past few decades, the death rate in 1946, the year of this study, was 80.3 per 100,000 persons, whereas the national tuberculosis mortality rate for the same year was less than 40. Among white persons in Baltimore, the death rate was 46.7 per 100,000; among Negro residents, who constituted one-fifth of the population and contributed 53 per cent towards the city's mortality from tuberculosis, the death rate was 218.7 per 100,000.

In an effort to expand its tuberculosis control activities, the Baltimore City Health Department began several years ago to explore the use of mass radiography of apparently healthy persons. In the summer of 1944, with the assistance of the United States Public Health Service and the Maryland Tuberculosis Association, the Bureau of Tuberculosis obtained the use of a mobile photofluorographic unit equipped to take 35 mm. films (changed in May 1946 for a 70 mm. unit). This unit has been in *continuous* operation since then and has been transported around the city taking chest roentgenograms of various groups of the population. By the end of 1947, approximately 155,000 supposedly healthy persons had been examined in 140 groups of the city's population.

METHOD OF INVESTIGATION

The material which has been selected for the purposes of this investigation is derived from the activities of the portable photoroentgen unit in Baltimore during the year 1946. At the time this study was undertaken, sufficient time

had elapsed to make possible final evaluation of the status of the cases found. Accordingly, the data for this year could be analyzed not only as to the results of survey film readings but followed through to determine those individuals who had active tuberculous disease requiring administrative attention.

During the calendar year 1946, fifty groups of apparently healthy people were examined roentgenographically in the mass survey program. A total of 48,175 persons were examined, roughly 5 per cent of the estimated total population of Baltimore City (930,000). The groups were selected by invitation and solicitation or on the basis of requests by the groups themselves. Since the service was not compulsory, only those persons who were interested in having a chest film, or could be persuaded to have one, were examined. There was no selection with respect to ability to pay as the service was free. The groups examined were industrial, office and department store employees, residents of housing projects and various communities, and students in the high schools and colleges. Approximately 80 per cent of the persons who were offered this service at their place of employment participated. The potential populations of the loosely defined "communities" were not known and the proportion examined undeterminable. All but three of the public high schools in the city were included in the 1946 surveys, and one vocational school as well, with participation close to 100 per cent.

Approximately two-thirds of all persons examined in 1946 were white (32,676) and one-third were Negro (15,499). The 2:1 ratio of white to Negro participants in the survey program represented a greater proportion of Negroes than was found in the general population of Baltimore City in which only 20 per cent of the inhabitants were Negro. Of the white people who were examined, 53.5 per cent were males and 46.5 per cent females; among the Negro participants, males constituted 45.3 per cent and females 54.7 per cent. The predominance of males over females among white persons examined and of females over males in the Negro group was due principally to differences in sex distribution in the schools. Sufficient data were not available to determine age distribution for the entire group, but participation of children of elementary school age and younger was discouraged, and elderly people did not participate to any considerable extent. However, despite the policy of discouraging young persons under the age of 15 years from entering into the program, it was found exceedingly difficult to adhere to this in the housing project and community groups and in high schools with lower grade components. If the percentage age distribution of similar groups surveyed in the first half of 1947 is applied to this study, it appears that approximately one-sixth of all persons examined roentgenographically in 1946 were in the age group 10 to 14 years.

Radiographic Reading and Classification of Cases

Interpretations of the small project films and readings of the follow-up 14 by 17 films were recorded according to a fixed classification. The diagnostic categories for miniature film interpretation were: negative, unsatisfactory, defi-

nite tuberculosis, suspected tuberculosis, or nontuberculous disease. Interpretation of the standard 14 by 17 inch celluloid films with respect to the diagnosis of pulmonary tuberculosis followed the National Tuberculosis Association's classification for extent of lesion: minimal, moderately advanced, and far advanced. The U. S. Public Health Service classification plus the reader's judgment were used for designating activity of the lesion: probably active, questionably active, and probably inactive.

All of the small film interpretations represented the impressions of a single examiner, one chest physician who had read all of the survey films since the unit program was initiated. The 14 by 17 film readings were the interpretations of several examiners, although the large majority of them were initially read or later reviewed by the same physician who interpreted the microfilms. There was not the same uniformity of interpretation of the large films because many individuals went to places other than the mobile unit to obtain them. When 14 by 17 films were taken at the city chest clinics, which was a frequent occurrence, the physical and laboratory findings on the clinic history were available to the film reader.

A case of tuberculosis found by survey was theoretically defined as one which was so diagnosed on the basis of the miniature and standard size films. The probably active and questionably active groups have, in this inquiry, been considered to constitute the group of clinically significant lesions, the group which would require treatment or observation. The probably inactive group is considered to be one which requires only re-examination with a roentgenogram one year after the survey film.

Final classification and disposition of all individuals whose microfilms had been read as not negative was made after consideration of all available post-survey data. For each person examined roentgenographically in 1946, there had been a post-survey period of observation of at least one year and a maximum of two years for some of them.

A case of tuberculosis discovered by survey was defined as one which had not been previously reported, which fulfilled residence requirements, and which had been reviewed and accepted by the Director of the Bureau of Tuberculosis as exhibiting changes in the lungs of tuberculous origin. *Discovered cases* were registered and enumerated in the annual morbidity statistics for the city. The evidence for registration of cases which were believed to require treatment or observation (the "clinically significant" cases) was generally based on history, certain clinical observations, and the roentgenogram and, in addition, one or more of corollary data such as tuberculin reaction, sputum or gastric washing examinations, and blood sedimentation rate. For those cases which were believed to require no more than a single re-examination with a roentgenogram at the end of one year, the "probably inactive" group, the evidence for registration was almost entirely roentgenological, *i.e.*, the appearance on the film of pulmonary changes which were considered consistent with a probably healed tuberculous process.

RESULTS OF SURVEY PROCEDURE

Frequency of Pulmonary Tuberculosis in the Total Surveyed Population

Analysis of the record cards of the 48,175 persons who received chest roentgenograms showed that 47,082 had essentially negative miniature films (97.7 per cent). There were 1,093 persons who had evidence of abnormality of some type or had technically unsatisfactory films. The project film readings of this group of 1,093 "not negative" films (2.3 per cent of the total number done) were as follows:

Unsatisfactory films	60 (0.1 per cent)
Nontuberculous pathology	371 (0.8 per cent)
Tuberculous pathology	662 (1.4 per cent)
Definite tuberculosis	202 (0.4 per cent)
Suspected tuberculosis	460 (1.0 per cent)

With the screening procedure of miniature filming alone, therefore, it was found that approximately one and one-half per cent of all persons examined had definite or suspected evidence of tuberculosis.

All of the persons whose small films showed definite or suspected tuberculosis were asked to return for further examination by means of a full-size film, and 86 per cent responded. Twenty-nine individuals whose microfilms had been interpreted as showing definite tuberculosis and 61 persons whose small films showed suspected tuberculosis did not return for full-size films. In addition to this group of "recalls," roughly one-third of the persons whose miniature films had shown signs of nontuberculous pathology were advised to have 14 by 17 films as it was believed that further roentgenological investigation would be desirable.

Altogether, 755 persons returned for re-examination with 14 by 17 films after initial miniature film screening. Among them, 348 cases of definite or suspected tuberculosis were found; the equivalent of 0.7 per cent of the total number radiographed. The results of their re-examinations are presented in table 1 correlated with the initial project film interpretations. If *all* persons whose microfilms had been read as "not negative" had been re-examined with 14 by 17 film, and definite or suspected tuberculosis found in the same ratio as presented in table 1, the frequency of these findings in the whole survey group would have approximated 0.8 per cent.

It may be seen that a second radiological examination reduced the tuberculosis findings by approximately one-half when comparison is made with the figure of 1.4 per cent based on project film interpretations. Had only one radiological examination been made, twice as many cases of definite or suggestive tuberculosis would have been reported in the mass surveys. In view of recent investigations demonstrating essentially equal intrinsic and extrinsic errors in the interpretation of films of all sizes (9, 13), it appears that a second roentgenological examination *per se*, and not the size of the film used in the re-examination, leads to considerable modification of initial film interpretation.

The number of *cases of definite tuberculosis alone* (*14 by 17 film readings*), exclusive of suspicious cases, represented 0.6 per cent of all persons examined, and the white group (0.7 per cent) and the Negro group (0.5 per cent) were similar. Approximately two-thirds of the definite tuberculous lesions were found to be minimal in extent and only one-third advanced, a finding that has been almost universal in the experience of mass surveys of supposedly healthy individuals. This ratio was exhibited in both the white and Negro population groups in this study.

Among the 292 cases of definite tuberculosis which were found, the extent and probable activity of the lesions were specified in 272 instances (table 2). Almost

TABLE 1

Correlation of Readings of Project Films and Re-examination by 14 by 17 Films, Mass Surveys, Baltimore, 1946

	PROJECT FILM IMPRESSION				
	Total	Unsatisfactory	Nontuberculous abnormality	Definite tuberculosis	Suspected tuberculosis
Project films with evidence of pathology or unsatisfactory	1,093	60	371	202	460
Total retakes on 14 by 17 films	755	16	167	173	399
14 by 17 film readings					
Essentially negative	257	15	43	5	194
Nontuberculous abnormality	150	0	112	5	33
Definite tuberculosis:	292	1	7	162	122
Minimal	189	1	5	79	104
Moderately advanced	88	0	0	76	12
Far advanced	8	0	0	7	1
Other tuberculosis	7	0	2	0	5
Suspected tuberculosis	56	0	5	1	50

one-half were considered *clinically significant* (0.3 per cent of the total number radiographed), and no essential difference was observed between the white (0.3 per cent) and Negro (0.2 per cent) groups. Approximately one-third of the persons found to have minimal lesions were classified as in need of treatment or observation. These minimal lesions of clinical significance comprised more than half of the total number regarded as clinically significant and 23 per cent of all the tuberculous lesions found. In the combined group of cases read as moderately advanced and far advanced, nearly two-thirds were diagnosed as in need of medical care. These moderately advanced and far advanced cases of clinical significance constituted almost one-half of the total interpreted as of clinical significance and 20 per cent of all the tuberculous cases found.

Most of the differences between white and Negro groups were on the borderline of statistical significance and may have been the result of certain limiting

factors, such as age or the knowledge of race by the film reader. No essential sex differences were noted. Since the age distribution of the total group surveyed was not known, age-specific rates could not be calculated.

Frequency of Pulmonary Tuberculosis in Constituent Groups Surveyed

Because the number of apparently healthy persons examined in each of the 50 groups which constituted the surveyed population in 1946 was too small for satisfactory analysis, it appeared advisable to combine comparable groups into larger units. Seven broad constituent groups emerged composed of individuals of similar occupation, place of residence, or place of study. Race distribution has been presented for these broad groupings, but sex distribution has not been included since the lack of age data in the material available for analysis placed serious limitations on the interpretations which could be made from sex data alone.

TABLE 2

Classification of 14 by 17 Films Read as Showing Tuberculosis, according to Extent and Probable Activity of Lesion, 1946

	ALL RACES		WHITE		NON-WHITE	
	Number	Per cent	Number	Per cent	Number	Per cent
Total read as tuberculosis	292		215		77	
Total with probable activity of lesion specified	272	100.0	206	100.0	66	100.0
Clinically significant	125	46.0	88	42.8	37	56.0
Probably inactive	147	54.0	118	57.2	29	44.0
Minimal	180	100.0	135	100.0	45	100.0
Clinically significant	68	37.8	45	33.3	23	51.1
Probably inactive	112	62.2	90	66.7	22	48.9
Moderately advanced and far advanced	91	100.0	71	100.0	20	100.0
Clinically significant	57	62.6	43	60.6	14	70.0
Probably inactive	34	37.4	28	39.4	6	30.0

Of the 32,676 white persons who were examined, one-third were high school or junior high school students. Industrial workers, office employees, and department store personnel accounted for another third; and the remaining 30 per cent was made up of residents of housing projects and various communities in the city, college students, and miscellaneous small groups. Of the 15,499 Negro individuals examined roentgenographically, almost one-half were high school or junior high school students. Approximately one-third were drawn from housing projects and different communities in the city, and only a small number were examined at their place of employment.

Comparison among the various survey groups was made with respect to the prevalence of "definite tuberculosis" and the frequency with which "clinically

significant tuberculosis" was found, as indicated by the result of interpretation of roentgenographic re-examination (14 by 17 films), and as shown in tables 3 and 4.

The percentage of *cases of definite tuberculosis* found in the various population groups ranged from 0.1 per cent among high school and junior high school pupils to 1.2 per cent among office personnel (table 3). The frequency of finding definite tuberculosis among industrial workers, office workers, department store employees, and residents of various communities was substantially similar and approximately 1.0 per cent. Examination of residents of housing projects yielded

TABLE 3

Distribution of Cases of Definite Tuberculosis (14 by 17 Film Readings) in Mass Surveys in Baltimore, 1948, according to Constituent Groups and Races

SURVEY GROUPS	TOTAL			WHITE			NON-WHITE		
	Number examined	Definite tuberculosis		Number examined	Definite tuberculosis		Number examined	Definite tuberculosis	
		Number	Per cent		Number	Per cent		Number	Per cent
All groups	48,175	292	0.6	32,676	215	0.7	15,499	77	0.5
Industrial	5,094	57	1.1	3,930	46	1.2	1,164	11	0.9
Business office	5,549	69	1.2	4,565	57	1.2	984	12	1.2
Department store	3,839	38	1.0	3,585	36	1.0	254	2	0.8
Housing project	4,922	28	0.5	2,147	12	0.6	2,775	16	0.6
Community	7,152	63	0.9	4,989	52	1.0	2,163	11	0.5
High School and Junior High School	17,960	19	0.1	10,720	8	0.1	7,240	9*	0.1
College	1,810	6	0.3	1,160	0	0	650	6	0.9
Miscellaneous	1,849	12	0.6	1,580	4	0.3	269	8	3.0

* Excludes 2 cases in Chinese.

0.5 per cent of definite cases, probably a reflection of the high proportion of children examined.

The findings among whites and Negroes were essentially similar for most of the groups. In community surveys, twice as many cases of definite tuberculosis were found among white persons (1.0 per cent) as among Negroes (0.5 per cent), a difference that was probably due to age distribution. Among college students, no cases were found in the white group and 0.9 per cent in the Negro group; the incompleteness of participation of the college students and the fact that the Negro students were almost all females may have accounted for this disparity.

Tuberculous lesions of clinical significance were found among all of the constituent groups, except the student groups, with essentially the same frequency (0.3 to 0.5 per cent) and no racial differences were observed. In table 4 are presented the findings for each of the groups.

Net Contribution to Tuberculosis Case Finding

To ascertain the full contribution of mass roentgenographic surveys to tuberculosis case finding, it is necessary to add to the cases directly found those which were diagnosed as a result of the follow-up investigations initiated by the survey findings. In addition to the 292 cases of definite tuberculosis found as an immediate result of the surveys, there were 35 cases similarly diagnosed as a result of later examinations. A total of 327 cases of tuberculosis, therefore, was the gross contribution of mass radiography in 1946.

To determine the role of mass surveys in the *discovery of new cases* of tuberculosis in Baltimore, the 327 found cases were subjected to the requirements for

TABLE 4

Distribution of Cases of Clinically Significant Tuberculosis (14 by 17 Film Readings) in Mass Surveys in Baltimore, 1946, according to Constituent Groups and Races

SURVEY GROUPS	TOTAL			WHITE			NON-WHITE		
	Number examined	Clinically significant tuberculosis		Number examined	Clinically significant tuberculosis		Number examined	Clinically significant tuberculosis	
		Number	Per cent		Number	Per cent		Number	Per cent
All groups	48,175	125	0.3	32,676	88	0.3	15,499	37	0.2
Industrial	5,094	21	0.4	3,930	16	0.4	1,164	5	0.4
Business office	5,549	21	0.4	4,565	18	0.4	984	3	0.3
Department store	3,839	20	0.5	3,585	19	0.5	254	1	0.4
Housing project	4,922	15	0.3	2,147	7	0.3	2,775	8	0.3
Community	7,152	22	0.3	4,989	17	0.3	2,163	5	0.2
High School and Junior High School	17,960	17	0.1	10,720	8	0.1	7,240	7*	0.1
College	1,810	3	0.2	1,160	0	0	650	3	0.5
Miscellaneous	1,849	6	0.3	1,580	3	0.1	269	3	1.1

* Excludes 2 cases in Chinese.

registration and the result is shown in table 5. Twenty-one of the cases were excluded because the diagnosis of tuberculosis was later withdrawn, 26 were excluded because of nonresidence in Baltimore City, and 70 were already known to the health department. The resultant net yield of discovered cases was 210, or 0.4 per cent of the 48,175 examinees. Approximately one-half of the discovered cases (99) were considered clinically significant, 0.2 per cent of the total number subjected to roentgenographic examination.

Minimal lesions formed more than two-thirds of all the new cases, but only one-third of the minimal lesions were considered of clinical significance. That is to say, cases of minimal tuberculosis requiring treatment or observation constituted approximately one-fourth of all discovered cases. Moderately advanced and far advanced lesions of clinical significance were discovered to substantially the same extent as the clinically significant minimal lesions.

Ratio of "discovered" cases to "all reported" cases: In table 6 are shown the number and type of cases of pulmonary tuberculosis discovered by mass sur-

TABLE 5

Cases of Definite Tuberculosis (including Clinically Significant and Inactive) Discovered as a Result of Mass Surveys in Baltimore in 1946, All Races

CLASSIFICATION	TOTAL NUMBER FOUND	NUMBER DIAGNOSIS REVISED	NUMBER NON-RESIDENT	NUMBER PREVIOUSLY REPORTED	DISCOVERED CASES		
					Total number discovered	Number clinically significnt	Number probably active
All types	327	21	26	70	210	99	111
Minimal	214	13	18	40	143	50	93
Moderately advanced	94	2	8	27	57	40	17
Far advanced	10	1	0	2	7	6	1
Primary (other)	9	5	0	1	3	3	0

TABLE 6

Ratio of Cases Discovered by Survey to all Reported Cases of Pulmonary Tuberculosis in Baltimore in the Year 1946.

CLASSIFICATION OF LESIONS	TOTAL NUMBER REPORTED	NUMBER OF TOTAL REPORTED BY SURVEYS	PERCENT OF TOTAL REPORTED BY SURVEYS	WHITE			NON-WHITE		
				Number reported	Number of total reported by surveys	Percent of total reported by surveys	Number reported	Number of total reported by surveys	Percent of total reported by surveys
All cases with extent of lesion classified	1,465*	210	14.3	865	148	17.1	600	60	10.0
Minimal. All types	503	143†	28.5	354	99	28.0	149	43	29.0
Active	202	50†	24.7	135	25	18.5	67	24	36.0
Inactive	258	93	36.0	209	74	35.4	49	19	39.0
Pleural effusion	43			10			33		
Moderately and far advanced. All types	849	64†	7.5	482	49	10.0	367	14	3.8
Severe primary lesions	78	3	4.0	18			60	3	5.0
Acute miliary or disseminated	35			11			24		

* Excludes 3 pulmonary cases with extent of disease and activity unspecified.

† Includes 1 case in Chinese.

veys in 1946 in relation to the entire year's morbidity notification from all sources.

In Baltimore in 1946, the diagnosis of pulmonary tuberculosis was accepted in 1,468 cases, including those discovered by survey. Minimal lesions of all types comprised 34 per cent of all reported pulmonary cases. Minimal lesions

designated as active (corresponding to the study classification of clinically significant) were reported in only 13.8 per cent of all new cases. Moderately advanced and far advanced cases in all stages of activity constituted 58 per cent of all notifications.

The 210 cases discovered by mass surveys contributed 14.3 per cent towards the total pulmonary cases reported.

In the group of active minimal cases, one-fourth (50) of the total number reported were the product of survey examinations. This represented a contribution of 18.5 per cent to the active minimal cases reported in white persons and more than one-third towards the total number of cases of active minimal tuberculosis in Negroes. Although the yield of 50 cases of clinically significant minimal tuberculosis from the examination of 48,175 individuals appears exceedingly small, the reporting of this type from all other sources in Baltimore was so slight as to make the survey contribution a considerable one.

Advanced cases of all types which were discovered by survey formed only 7.5 per cent of the year's reported cases in this classification.

It was not possible to thoroughly investigate the discovered cases to determine how many of them could have been reported through other channels, had these other channels functioned more efficiently. However, a superficial investigation was made of one-half of the 99 discovered cases of clinical significance. It was found that 5 of the clinically significant discovered cases were contacts of active or fatal cases known to the health department (3 minimal and 2 moderately advanced); these cases could have been found by methods other than survey, such as more intensive nursing and clinic follow-up. There were in addition 5 cases which were known to hospital dispensaries or private physicians but had never been reported to the official agency. These cases could have been known to the health department without benefit of survey only if reporting by private physicians and general hospitals were improved.

On the basis of these incomplete data, it appears that approximately 10 per cent of the discovered cases of clinical significance could have been found by improved contact examinations, and 10 per cent were already under the supervision of private physicians or hospitals, although unknown to the health department.

It would be of considerable interest to examine the reported cases of respiratory tuberculosis in former years in Baltimore to determine whether there had been a change in the ratio of early to advanced cases since the advent of mass radiography of supposedly healthy individuals. Unfortunately, the tuberculosis morbidity statistics before the year 1943 do not include a description of extent and probable activity of tuberculous lesions. A review of the five-year period, 1943–1947, however, can offer some points of interest.

The period 1943–1947 was one of continuous tuberculosis case finding by means of mass radiography. In 1943 the activities of the military induction stations in Baltimore were at their height and all cases of tuberculosis found in persons examined for military service were reported to the Baltimore City Health Department. In 1944, while military examinations were continuing at a

good pace, the mobile photoroentgen unit of the Baltimore City Health Department went into operation and by 1945, when reports from the induction stations were diminishing, the results of the mobile unit's activity were becoming apparent.

In 1944, the number of persons examined by the induction centers plus those examined by the mobile unit equalled the number examined for military service in 1943. During the subsequent three years, almost all radiography was done by the mobile unit (examinations for military service ceased in October 1946) and the number of persons examined in each of the three years was greater than during 1943 or 1944.

Nevertheless, the number of reported cases of active minimal tuberculosis, which had been high in 1943 and at its peak in 1944, declined sharply after 1944, and the ratio of reported active minimal cases to advanced cases declined in

TABLE 7

Ratio of Reported Cases of Active Minimal Tuberculosis to Reported Cases of Advanced Tuberculosis, all Types, Baltimore, 1943–1947

YEAR	TOTAL			WHITE			NON-WHITE		
	Number minimal tuberculosis active	Number advanced tuberculosis all types	Ratio of active minimal to advanced. All types	Number minimal tuberculosis active	Number advanced tuberculosis all types	Ratio of active minimal to advanced. All types	Number minimal tuberculosis active	Number advanced tuberculosis all types	Ratio of active minimal to advanced. All types
1943	322	1,070	0.30	191	596	0.32	131	474	0.28
1944	378	961	0.39	242	542	0.45	136	419	0.32
1945	228	936	0.24	151	561	0.27	77	375	0.20
1946	202	849	0.24	135	482	0.28	67	367	0.18
1947	157	894	0.18	95	485	0.19	62	409	0.15

parallel fashion. This is illustrated in table 7 for the white and Negro populations of Baltimore. During the same five-year period, deaths from pulmonary tuberculosis decreased among white residents but Negroes experienced no essential change.

It appears that mass radiography, as practiced in Baltimore by the mobile unit, did not uncover as many cases of active minimal tuberculosis as did the *compulsory and complete* screening of an adult male group of the population, selected only with respect to age. Although large numbers were examined by the mobile unit, groups which are generally found to have a high tuberculosis rate, such as unemployed and homeless men (who were compelled to be examined by the induction stations), were not systematically included; and, on the other hand, many children participated and they were found to have very little tuberculosis.

The yield of the mobile unit's activities in finding active minimal tuberculosis appears also to have diminished during the three and one-half years of its operation. The repetition of surveys of certain groups, four groups in 1946 and almost a dozen in 1947, probably diminishes the returns of case finding if the groups are fairly stable and those re-examined are the same people.

Disposition of Discovered Cases of Tuberculosis

Information concerning the provision of medical care for the newly discovered cases was gathered from the files of the Baltimore City Health Department for the maximum post-survey observation period possible in this inquiry, the twenty-four months from January 1946 to December 1947. The absence of follow-up data in the health department records did not necessarily mean that no further examinations had been made but rather that further observations were not known to the health department.

TABLE 8

Follow-up Observations of Cases of Pulmonary Tuberculosis Discovered in Mass Surveys in Baltimore in 1946 during a Two-year Post-survey Period

	TOTAL				WHITE				NON-WHITE			
	All cases	Minimal clinically significant	Minimal inactive	Advanced all types	All cases	Minimal clinically significant	Minimal inactive	Advanced, all types	All cases	Minimal clinically significant	Minimal inactive	Advanced, all types
Number discovered cases	210	49	93	63	148	25	74	49	57*	24	19	14
Number having some follow-up	112	40	31	41	68	18	23	27	44	22	8	14
Number having follow-up 1 year or more	89	32	24	33	52	14	18	20	37	18	6	13
Number found active at any time	32	6	3	21	13	1	2	10	17	5	1	11
Number hospitalized	32	13	2	15	12	4	1	7	17†	9	1	7
Number of deaths	4			4	1			1	2‡			2

* Excludes 3 cases of primary tuberculosis in Negroes and 2 cases of pulmonary tuberculosis in Chinese.

† Excludes 2 cases of primary tuberculosis in Negroes and 2 cases of pulmonary tuberculosis in Chinese.

‡ Excludes 1 case in Chinese.

Total includes 3 cases of primary tuberculosis in Negroes and 2 cases of pulmonary tuberculosis in Chinese.

A summary of the follow-up observations during 1946–1947 on the cases of tuberculosis discovered by the survey method is shown in table 8.

Of the 210 discovered cases, 98 cases, or 46 per cent, were not known to have had follow-up examinations after survey. Most of these had been originally classified as inactive. Of the 18 clinically significant cases without recorded follow-up observations, the majority were said to be under the care of private physicians. The only definite information which could be presumed about cases without known subsequent examinations was that they did not enter a sanatorium or die of tuberculosis in Maryland.

In describing the post-survey condition of the 112 cases who had follow-up examinations, certain definitions and assumptions have been made. Because of lack of uniformity in follow-up data and because of the paucity of cases in certain classifications, two broad classifications of condition after survey have been set up. *Active* includes all cases so described, all cases showing progression, all hospitalized cases for whom activity status was not known, and all fatal cases. *Inactive* includes all findings so described, all examinations which were said to show no change, and all findings which were said to show regression or clearing of lesions (although any change represents activity, the direction in these cases was towards improvement and they were, therefore, included with the "favorable" cases).

Of the 112 cases which had some follow-up, there were 31 which were found to be active at some time during the post-survey observation period, and in almost each case this decision was reached within six months after the survey film was taken.

The infrequency with which minimal lesions diagnosed as clinically significant were later found to show evidence of activity is noted. In fact, there appears to be no noteworthy difference between the proportion of active cases resulting from those originally called clinically significant and those initially diagnosed as probably inactive. However, considering the fact that the "no follow-up" group consisted largely of cases called inactive, and the "follow-up" group contained a majority of clinically significant cases, the lack of difference might not have been so apparent if the "no follow-up" group could have been included.

The seeming inocuousness in white persons of minimal lesions which appear to be roentgenologically clinically significant is quite interesting. Only one of the 18 clinically significant minimal cases which had follow-up later showed signs of activity. The proportion was considerably higher among Negroes, but even in this group only 5 out of the 22 clinically significant minimal cases in Negroes showed evidence of activity.

Hospitalization: One of the problems frequently mentioned in connection with mass radiography programs is the difficulty of providing institutional care for the tuberculosis cases which would be uncovered, particularly in areas where sanatorium facilities are inadequate, as in the state of Maryland.

The follow-up records of the cases of tuberculosis found by survey in 1946 show that 32 of the 210 newly discovered cases and 12 of the 70 previously known cases were hospitalized at some time during 1946 and 1947. The addition of 44 cases to the sanatorium load of Baltimore City over a period of two years does not indicate that survey activities as conducted by the Baltimore City Health Department produced a problem of hospitalization of serious proportions.

One year after survey, two-thirds as many Negroes who had been discovered to have lesions requiring treatment or observation had been hospitalized (45 per cent) as had white persons in similar condition. One white person and one Negro whose pulmonary lesions were regarded as inactive were hospitalized seven to eight months after survey.

Deaths: There were 5 persons found by survey to have tuberculosis during the year of 1946 who succumbed to the disease before the end of 1947. Two of the fatal cases were white, 2 were Negro, and one was Chinese. All had advanced pulmonary disease when first examined. Four of the 5 cases were newly discovered, one was already known to the health department.

DISCUSSION AND SUMMARY

This analysis of the experience of the Baltimore City Health Department with the application of mass radiography to some fifty groups of the population, constituting 48,175 apparently healthy persons, or about 5 per cent of the population, has revealed a net yield of tuberculosis cases which appears quite modest in relation to the effort expended. From an epidemiological viewpoint, the effectiveness of this part of Baltimore's tuberculosis-control program can be measured not by the number of individuals whose films showed evidence of tuberculous lesions but by the number of individuals who were discovered to have lesions which were of clinical significance, requiring medical supervision and care.

In the material which has been analyzed, it is interesting to note the manner in which the number of persons classified as having "definite or suspected" tuberculosis as a result of the reading of miniature films decreased through successive steps in the screening process. Re-examination by large film of all those who could be persuaded to return (86 per cent) reduced the number from 662 to 292 as having evidence of definite tuberculosis, and of these only 125 were thought to have lesions which were of clinical significance. When, however, these individuals were further processed, taking into consideration other clinical evidence and eliminating those who were nonresidents or had been previously reported, the number of cases remaining which were classified as having tuberculosis was 210, and of these 99 were thought to have an active disease process. Of the 210, the health department was successful in following 89 for a year or more. There were only 32 which were found to have unquestioned clinical activity, almost all of whom were hospitalized, and 4 of whom died. An unknown additional number were under private care.

As was stated in the introduction, one of the primary objectives of mass roentgenographic examinations is to increase the proportion of cases discovered in the minimal stage which are of clinical significance. The net yield in this respect was somewhat disappointing. Out of 1,468 cases of pulmonary tuberculosis which came to official attention during the year, only 202 were classified as active minimal, and of this latter number approximately one-fourth were contributed as a result of survey activity. That is to say, in spite of considerable effort expended in mass surveys, the proportion of new cases which were discovered in the active minimal stage was not materially increased. It may be that rather meager results are to be expected, since the screening process begins with a *single* microfilm observation on a single day on each individual. A film that was negative on this occasion might have been positive several weeks later. Moreover, the significance of minimal lesions thought to be active because of

roentgenographic appearance still remains to be elucidated. The development of better diagnostic techniques than are now available is needed before those lesions that are important from the point of view of possible progression can be definitely separated from those that are unimportant and will regress spontaneously without medical care.

The effort to find population groups which were contributing unusually to the tuberculosis problem of the community was unsuccessful. In fact, so far as could be judged from the data available, the frequency of positive findings was surprisingly similar in all of the adult groups which were surveyed. The only significant differences noted were the lower rates which were found in the school groups which were composed largely of adolescents. Only crude comparisons could be made, however, because age-sex specific rates could not be calculated. The obvious effect of selection makes the use of prevalence rates obtained in these survey groups unreliable as a basis for estimating the prevalence of the disease in the city as a whole.

Whether or not mass roentgenographic examinations of *all* kinds of groups of apparently healthy persons who can be easily and readily assembled should be continued remains to be determined. One possible modification of policy is to concentrate this effort more completely on *adult* groups living and working in the poorer and more crowded sections of the city, and especially to seek out adult Negro groups. While the prevalence in the two races is much the same, the significance of discovery of cases among Negroes differs from that of similar findings among whites since Negroes display the most pronounced tendency towards rapid, fatal progression of tuberculous lesions.

It also remains to be determined whether, in a community where tuberculosis is a major problem, an intensification of the search for new cases among the household associates and social and occupational contacts of known open cases may not yield a greater return for effort expended. A very superficial investigation in the course of this study revealed the fact that at least 10 per cent of the cases discovered by survey might have come to attention through other channels.

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THE SUITABLE DOSE OF TUBERCULIN FOR SINGLE TEST TUBERCULIN TESTING[1]

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INTRODUCTION

Tuberculin has long been used in two doses for testing purposes and those who do not react to the second dose are considered to be uninfected with the tubercle bacillus. Recently, evidence has been shown by those working in this field that there are very likely some factors causing nonspecific reaction when a too large dose of tuberculin is used. This hypothesis of nonspecific reaction is supported by Furcolow, Hewell, Nelson, and Palmer's well planned experiment (1) in which they found that the dose five times the first dose (1 T.U.[2]) used in the traditional two-dose tuberculin testing is sufficient for all purposes of diagnosing tuberculous infection, and nonspecific reactions are liable to be elicited with larger doses. Seibert also holds the same opinion (2). Hsueh and Ch'iu in 1941 showed that 0.00025 mg. of PPD (12.5 T.U.) could be safely used for single dose testing (3). Apparently European workers are of similar opinion for the WHO-ICEF recommendation (4) of the final dose of tuberculin for pre-BCG tuberculin testing is to be 10 T.U.

The present report deals with a comparison of results with 10, 50, 100, and 250 T.U. in Chinese children to find out the most suitable dose of tuberculin that can be used for single dose testing.

MATERIAL AND METHOD

As nearly all the people above the age of twenty years of age in this city are infected with the tubercle bacillus, school children were selected as the test population. The total number of children tested was 5,512, aged between four and sixteen years, students at ten primary schools in the First Health District of Peiping. The tuberculin used was PPD, a commercial product of Parke, Davis and Co. It was used according to the manufacturer's direction without further standardization. The doses used were as follows:

0.000,02 mg.	1 T.U.	
0.000,2 mg.	10 T.U.	
0.001 mg.	50 T.U.	
0.002 mg.	100 T.U.	
0.005 mg.	250 T.U.	all in 0.1 cc. solution.

All the children were first tested with 1 T.U. Those who did not react were given a second test with the other four doses injected at one sitting. The first dose was injected on the middle portion of the flexor surface of the left forearm.

[1] From the Department of Public Health, Peiping Union Medical College and the Peiping Tuberculosis Center, Peiping, China.

[2] T. U. = Tuberculin unit. 1 T. U. = 1/100 mg. of O. T., or 0.000,02 mg. of PPD.

The four doses of the second test were injected on the flexor surface of both forearms, with 10 and 250 T.U. on the left and 50 and 100 T.U. on the right. The two injections on one arm were made three inches apart. The results were read at the end of forty-eight hours, the criteria being as follows:

Induration	*Result*
5 to 10 mm.	+
10 to 20 mm.	++
20 mm. and over	+++
Ulcer or blister	++++

TABLE 1

Number of Reactors to Various Doses of the Second Test

AGE	SECOND TEST																					
	10 T. U.					50 T.U.					100 T.U.					250 T.U.					Number of reactors to second test	10/250 T.U.
	+	++	+++	++++	Total	+	++	+++	++++	Total	+	++	+++	++++	Total	+	++	+++	++++	Total		
																						per cent
4																						
5	3				3	1	2			3	1	1			2	1	1	2		4	4	75.0
6	17	1			18	15	7			22	16	10	2		28	14	10	5		29	29	62.1
7	29	15			44	11	31	6		48	14	30	11		55	25	15	28		68	68	64.7
8	45	23	1		69	24	44	10		78	22	43	23		90	23	33	39		95	95	72.7
9	61	16	2		77	33	44	12		89	32	59	25		100	16	38	45		99	100	77.8
10	56	23	3		82	32	46	18		96	16	61	28		103	18	52	42		112	112	73.2
11	50	30	4		92	26	65	17		108	27	51	32	1	121	29	43	57	1	130	130	70.7
12	57	22	5		84	20	53	22		95	5	36	39		95	9	36	55		100	100	84.0
13	59	23	4		66	12	40	19		71	8	3	29		73	7	24	44		75	75	88.0
14	4	3			7	3	2	3		8	1		4		8	1	3	5		9	9	77.8
15	4				4	1		1		2	1		1		2	1		1		2	4	—
16																						
Total.....	373	156	19		548	174	332	168		620	139	339	192	1	677	141	254	321	1	723	726	75.8

Only induration was measured; redness without induration was not considered as significant. All readings were made with extreme care to avoid any possible false reaction.

RESULTS

Of the 5,512 children tested with 1 T.U., 2,100 did not react to it. These nonreactors were further tested with four doses of 10, 50, 100, and 250 T.U. The number of reactors to the various doses are shown in table 1.

Among the 2,941 who received the second test, there were 548, 620, 677, and 723 who reacted to 10, 50, 100, and 250 T.U., respectively. If the number of

reactors to 250 T.U. is considered to be 100 per cent of those who would react to tuberculin, then the 10, 50, and 100 T.U. doses are capable of eliciting 75.8, 85.7, and 93.6 per cent of reactors, respectively.

Since the figures in table 1 only represent the results obtained from the non-reactors to the first test, it is more rational, in comparing the results of 10, 50, 100, and 250 T.U., to add the number of reactors to the first test to the numbers of reactors in table 1.

TABLE 2

Accumulated Number of Reactors to the Various Doses

AGE	TOTAL NUMBER TESTED	REACTORS TO VARIOUS DOSES										
		1 T.U.		10 T.U.		50 T.U.		100 T.U.		250 T.U.		10/250 T.U. per cent
		number	per cent	number	per cent	number	per cent	number	per cent	number	per cent	
4	2	1	—	1	—	1	—	1	—	1	—	—
5	39	10	—	13	—	13	—	12	—	14	—	—
6	432	129	29.9	147	34.0	151	35.0	157	36.2	158	36.6	93.0
7	656	253	38.6	279	42.5	301	45.9	308	47.0	321	48.9	86.9
8	859	344	40.0	413	48.1	422	49.2	434	50.5	439	52.3	94.1
9	734	352	48.2	429	58.5	441	60.1	452	61.5	451	61.4	95.1
10	861	434	50.5	516	59.9	530	61.5	537	62.2	546	63.4	94.5
11	778	429	55.2	521	67.0	537	69.0	550	70.7	559	71.9	93.1
12	599	371	61.9	455	76.0	466	77.8	466	77.8	471	78.6	96.5
13	405	253	62.5	319	76.3	324	80.0	326	80.5	328	81.0	97.2
14	129	97	75.2	104	80.6	105	81.4	105	81.4	106	82.2	98.1
15	16	11	—	15	—	13	—	13	—	13	—	—
16	2	2	—	2	—	2	—	2	—	2	—	—
Total....	5,512	2,686	48.9	3,214	58.3	3,306	60.0	3,363	61.1	3,409	61.8	94.3

From table 2 it is shown that among the 5,512 children tested, 3,214 reacted to 10 T.U. while 3,306, 3,363, and 3,409 reacted to 50, 100, and 250 T.U., respectively, which means that the 10, 50, and 100 T.U. doses can yield 94.3, 97.0, and 98.7 per cent of reactors as compared with the number of reactors to 250 T.U.

DISCUSSION

In epidemiological work the two-dose tuberculin testing has been found to be very inconvenient. This inconvenience can be eliminated if a suitable dose of tuberculin can be found which, when used as a single test, can yield enough significant reactors without causing too many severe reactions. As it is known that the first strength (1 T.U.) used in the two-test tuberculin testing can yield only about 50 per cent reactors and a certain number of nonspecific reactions are elicited by the traditional second strength (250 T.U.), the suitable dose of tuberculin for a single test must lie between one and 250 T.U. As shown by the data in table 2, 10 T.U. are capable of yielding 94.3 per cent of all reactors to

250 T.U. and causing probably no more than 4.6 per cent of severe reactions (++++) (3); though 50 and 100 T.U. can yield a few more reactors, they are statistically nonsignificant and even less desirable when nonspecific reactions are taken into account. The difference between numbers of reactors to 10 and 250 T.U. is so small that it is only barely significant, and in two-test tuberculin testing there will be 50 per cent nonreactors to the first test who have to receive a second test of 250 T.U. (in Denmark 100 T.U.). The average amount of tuberculin used on each person will be around 125 T.U. In epidemiological work the material and time thus saved would be quite considerable. So it is our opinion that 10 T.U. can be considered as the suitable dose of tuberculin for single-dose tuberculin testing.

SUMMARY

1. An experiment to find out the suitable dose of tuberculin for single-test tuberculin testing was made in a test population consisting of 5,512 primary school children between four and sixteen years of age.

2. Ten T.U. of tuberculin (PPD tablets) were found to be capable of yielding 94.3 per cent of all possible reactors to 250 T.U. and can be recommended as the suitable dose of tuberculin for single-test tuberculin testing.

SUMARIO

La Dosis Adecuada de Tuberculina para la Comprobación con Reacción Unica

1. Este experimento tenía por objeto descubrir la dosis adecuada para la comprobación con tuberculina en una sola reacción.

2. La población comprobada constaba de 5,512 alumnos de las escuelas primarias, de 4 a 16 años de edad.

3. Diez Unidades de Tuberculina resultaron suficientes para descubrir 94.3 por ciento de todos los posibles reactores a 250 Unidades de Tuberculina, de modo que puede recomendarse esa dosis como adecuada para una sola comprobación con tuberculina.

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DISPOSITION AND FOLLOW-UP OF PULMONARY TUBERCULOSIS[1]

A Study Based on the Character and Extent of the Lesion Seen on the Initial Roentgenogram

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INTRODUCTION

This report is made because it is believed that: (*1*) the clinical course and outcome can be forecast for a group of persons whose tuberculosis is detected in a routine roentgenological chest survey; and (*2*) the preliminary disposition can be determined in a large percentage of the cases on the basis of the classification and interpretation of the original roentgenogram. It should be emphasized that, while the group prognosis can be predicted with reasonable assurance, there will be some individual exceptions. Consequently, the family physician who deals with and makes prognoses for patients must take this into consideration and keep this limitation in mind.

It must be remembered that prior to the widespread use of roentgenograms in the search for pulmonary tuberculosis in the general population, most cases of proved tuberculosis were found in the advanced stage when, unfortunately, symptoms were typical and usually there was no question about the treatment which was necessary. As routine chest roentgenograms came into more general use, lesions were found in the lungs of apparently healthy persons most of whom were asymptomatic. It was evident at once that it was of the utmost importance to determine the significance of these lesions, although there was little or no knowledge available to assist in the disposition of the individual case. After twenty years of continued observation and study evidence has been accumulated which appears to be at least a partial solution of this problem.

OBSERVATIONS

Development of Evaluation Procedures

Because pulmonary tuberculosis was a problem among employees, the Metropolitan Life Insurance Company began in 1927 to use the fluoroscope as a routine case-finding method. Since then all applicants for employment at the home office of the company have had a fluoroscopic examination of the chest as part of the pre-employment physical examination and all who showed suspicious or positive findings were examined roentgenographically at once. Since 1935 all applicants for employment have had both a fluoroscopic and roentgenographic examination. When lesions of the lungs were found, the applicant was re-examined and referred to his own physician or a clinic for further study and advice.

Because of the excellent immediate results in bringing to light hitherto unsus-

[1] From the Medical Department, Metropolitan Life Insurance Company, New York, N. Y.

pected cases, early in 1928 a routine fluoroscopic examination became a part of the annual physical examination of every home office employee. A chest roentgenogram was obtained if an employee had suggestive findings by fluoroscopy, significant symptoms, abnormal physical signs, or history of tuberculous contact. Furthermore, he was kept under close medical supervision which included repeated roentgenograms.

As soon as fluoroscopic examinations were started as a routine procedure, cases were detected which had roentgenological evidence of what once must have been disease of considerable extent and probably tuberculous in character but, upon discovery, had the appearance of a well-stabilized process. A less familiar type of lesion was also discovered, a small circumscribed homogeneous hazy or mottled area of an entirely different character than those just described. In addition, as would be anticipated, lesions of an unquestionably dangerous nature were also found. Even in the beginning it was believed that any abnormal finding on the chest roentgenogram should not be dismissed lightly, but it seemed probable that not every person under consideration needed treatment. In many instances it was perplexing to know when it was safe to wait for the development of further evidence and information, and when it was unsafe to wait.

During the first few years of routine fluoroscopy at the annual examination of employees, 139 had chest roentgenograms which were classified as: apparently arrested tuberculosis (males, 87, females, 52) minimal, 120; advanced, 19. These were found among apparently healthy people at work, practically all of whom had been with the company since leaving school. Nevertheless, after close questioning and careful examination the examiners were convinced that these individuals had not been aware of any serious or prolonged illness and their records showed that they had not been away from work for any length of time. Especially noteworthy was the absence of symptoms, physical signs, or positive laboratory evidence to account for or to corroborate the fluoroscopic and roentgenographic findings. The need for new criteria to determine the correct disposition of these cases was immediately apparent. As these persons were observed and experience increased, it became apparent that some of them had been able to resist a tuberculous involvement without being "sick" in the usual sense of the word. Moreover, some persons whose first roentgenograms showed a small hazy or mottled area remained well and the lesion cleared rather promptly during the period of observation, while others, in time, proved to have active, progressive tuberculosis. These observations raised the question whether it might be possible to predetermine which cases ultimately would do well or badly and which needed a relatively short period of careful observation to determine the trend.

As the case-finding work progressed, a routine system for studying each individual and recording the findings was developed and more was learned about the pitfalls in the problem of disposition. When a roentgenogram disclosed a lesion the employee was questioned carefully about his family and personal history, particularly in regard to the possibility of tuberculous contact. A physical examination was made by a trained chest specialist,[2] the sputum, if present, was

[2] Dr. Ada Chree Reid has carried out the advisory and supervisory clinical work referred to among home office employees.

examined, and during the period of evaluation roentgenograms were repeated at short intervals. It was unusual to find tubercle bacilli since only a few persons had expectoration and refinements of examination in general use today were unknown or unavailable when the majority of the cases were detected. It was soon learned that little diagnostic or prognostic importance could be attached to fluctuations in body weight. Active and newly developing lesions were found in employees, some of whom were gaining and some losing weight, and such changes were disregarded. It became apparent, too, that age, sex, weight, absence of physical signs, negative laboratory reports, and most symptoms were generally of little help in determining disposition. Consequently more and more reliance was placed on roentgenographic findings. Experience with employees treated at the sanatorium at Mount McGregor since 1914 had revealed that patients with minimal lesions fared much better from the standpoint of morbidity and mortality than those with advanced disease, but this knowledge was not particularly helpful in itself. Some of the lesions which seemed to be well stabilized and proved to be relatively insignificant were advanced in extent, and some of the lesions which were small upon detection proved to be, or progressed into, active tuberculous disease.

After all reports were assembled, a clinical recommendation was made to the employee: (*1*) to continue at work and follow all normal activities during careful periodic medical observation and supervision; or (*2*) to continue at work temporarily while undergoing special studies, usually with activity restricted; or (*3*) to enter a hospital or sanatorium immediately.

If sanatorium care was indicated, it was available at the company sanatorium at Mount McGregor without cost to the employee. While in the sanatorium the employee not only received care and treatment, but disability benefits to which he was entitled under his group insurance contract. He knew too that he would be re-employed upon successful completion of cure. If sanatorium treatment did not seem to be indicated at once, the employee continued at work under medical supervision by Doctor Reid, thus permitting the acquisition of further information and the evaluation of all the evidence before making a final decision.

In many cases it was found difficult to convince an employee, his family, or his private physician of the necessity for sanatorium treatment or medical supervision when the decision was based largely on roentgenographic findings. As a matter of fact, the first case of this type admitted to the sanatorium at Mount McGregor caused some consternation to the staff because it could not be diagnosed at that time as a case of pulmonary tuberculosis according to the Sanatorium Association and National Tuberculosis Association classification, despite the fact that no other diagnosis seemed tenable.

It is well known that an acceptable classification of the *extent* [3] of involvement has been available and has been in general use for years. But a satisfactory classification of the *character* of the lesion has not been adopted for many reasons,

[3] "Extent" of pulmonary lesions (minimal, moderately advanced, far advanced) as defined in the Diagnostic Standards and Classification of Tuberculosis of the National Tuberculosis Association.

although physicians caring for tuberculous patients routinely evaluate this feature. There have been marked differences in appraisal, terminology, and judgment in interpretation, and attempts to read pathological characteristics and implications into the wide variety of densities and shadow patterns have added

TABLE 1

Roentgenographic Classification and Insurability

CLASSIFICATION OF LESION BY ROENTGENOGRAM	ROENTGENOGRAPHIC APPEARANCE	RECOMMENDATION
Inactive	Extent: Any minimal or moderately advanced (N.T.A.) Character: Fine or coarse strands; small or large calcific densities; small opaque areas with borders clearly outlined. May be localized or scattered. *No cavities present.*	Insurable
Active	1. Extent: Minimal (N.T.A.) Character: Areas of cloudy mottling or homogeneous densities; borders hazy or not clearly defined. No suggestion of cavity	Uninsurable
	2. Extent: Moderately advanced (N.T.A.) Character: Areas of cloudy mottling or homogeneous densities; borders hazy or not clearly defined; cavitation not in excess of 4 cm. in diameter.	Uninsurable
	3. Extent: All far advanced (N.T.A.)	Because of the recognized heavy mortality in the far advanced group, all such cases were classed as active, *i.e.*, uninsurable.

to the confusion. These and other difficulties have no doubt delayed the acceptance and inclusion of the *character* of a lesion into a useful and workable classification.

Necessity, however, forced the development of a system of consistent appraisal of roentgenograms submitted by applicants for life insurance in whom there was a question of pulmonary tuberculosis. When a person applies for life insurance a decision to insure or not to insure must be made; there is no middle ground.

Therefore, in 1930 a classification for roentgenograms of the chests of applicants for insurance was adopted and three descriptive categories were used: (a) average healthy chest, *i. e.*, no evidence of disease, insurable; (b) inactive tuberculosis, insurable (table 1); and (c) active tuberculosis, uninsurable (table 2).

Inevitably there are some films which fall somewhere between the arbitrary divisions b and c. In such instances, the examiners used their best judgment as to whether the appearance seemed to be more or less favorable and made a decision as to insurability in each case.

Identification of Evidence of Value in Prognosis

Although a modus operandi for employees, applicants for employment, and applicants for life insurance, had been developed, the question arose whether it

TABLE 2

Description of Lesion, Age, Sex, and Disposition at Diagnosis of Pulmonary Tuberculosis

SEX CHARACTER OF LESION BY ROENTGENOGRAM* AGE	TOTAL	DISPOSITION	
		Continued at Work	Began to Cure
Total	592	308	284
Males	206	147	59
Inactive			
Under age 35	32	25	7
Age 35 or over	68	67	1
Questionably active			
Under age 35	37	16	21
Age 35 or over	39	34	5
Active			
Under age 35	25	4	21
Age 35 or over	5	1	4
Females	386	161	225
Inactive			
Under age 25	35	17	18
Age 25 or over	69	60	9
Questionably active			
Under age 25	143	41	102
Age 25 or over	82	38	44
Active			
Under age 25	43	4	39
Age 25 or over	14	1	13

* See Table 6.

was possible to find and identify evidence that would indicate what type of newly found lesions would do well or would do badly. If this were possible, it would be invaluable in the perplexing question of disposition. It is believed that this report on the analysis of the experience with this group of employees and applicants for life insurance gives a workable answer.

The clinical program among home office employees was carried out by Dr. Reid and has been described fully elsewhere (1, 2). The disposition of each case was made and carried out in accordance with conservative clinical judgment. Some employees continued at work, some began to cure, and at a later date a

few died. So far this is simply the usual story of any large group of tuberculous people followed for a long period of years.

The importance of the present report, however, is in the relationship between the clinical course and outcome, and the classification of the original chest roentgenogram. Two of the writers (J.A.E. and H.H.F.) independently classified the initial film without reference to the medical chart and without knowledge of the clinical aspects of the case. There was an agreement of classification between these two examiners of over 90 per cent. In all cases of original disagreement a conference resulted in a classification by agreement. There has been considerable recent discussion and question of the ability of roentgenologists to agree either with themselves or with others on classification, but without entering this discussion the writers are reporting their own experience.

After the roentgenograms were classified and after the clinical course was well established, the correlations and statistical analyses were made (M. G. S.). A special study card was prepared for each case showing the initial findings, the course, and outcome chronologically. The changes evident by serial roentgenographic examinations, *i.e.*, softening or hardening, increase or decrease, or stability, were plotted by one of the writers (H. H. F.). The clinical data (which had been entered on the medical chart whenever the patient was seen) were summarized and transferred to the study card strictly according to rules previously prepared. Thus the progress of each individual could be visualized at a glance. Statistical analyses were made of the relationship between the various factors. It cannot be emphasized too strongly that this compilation and analysis of the material was made objectively. Judgment concerning the lesions on the roentgenogram and selection of the pertinent clinical data were not modified by hindsight or by knowledge of the final outcome of the case.

Employee group: The employee group is made up of 592 Metropolitan Life Insurance Company personnel whose lung lesions were discovered under the program of tuberculosis detection and control. None had a previous history of tuberculosis; 99 had had a previous roentgenographic examination considered negative for tuberculosis, and 493 had had no previous roentgenogram of the chest. After detection, all were under medical supervision by Dr. A. C. Reid from one to twenty years and had repeated roentgenographic examinations.

The factors studied include: character and extent of the initial lesion, physical signs, symptoms, weight, sex, age, and disposition at time of diagnosis. The follow-up observations include: interval changes in the roentgenographic appearance, *i.e.*, softening or hardening, increase or decrease, or stability; status of the employee, *i.e.*, whether at work or able to work, curing, or dead; continued or subsequent signs, symptoms, or changes in weight; and surgical procedures for tuberculosis.

RESULTS

In the first analyses the material was divided into five-year age groups and subdivided by sex and roentgenographic classification. These groups varied so in size (from one case to 123 cases) that no valid conclusions could be drawn. It was

noted, however, that in general the younger people had a poorer outcome than the older people. Therefore, the material for each sex was divided into two halves. This resulted in groupings of males under age 35, and age 35 or over, at the time of the initial roentgenogram, and for females under age 25, and age 25 or over. The designation of younger and older groups in the subsequent discussion is used for these divisions. The ratio of males to females or the ratio of younger to older people has no significance because the age distribution of the employee group in which these cases were found does not conform to a standardized population.

Table 2 shows the distribution of the group at the time of diagnosis by sex, age, roentgenographic classification, and disposition. Slightly over half of the employees continued at work after diagnosis and the remainder began to "cure."[4]

TABLE 3

Signs or Symptoms at Diagnosis

SIGNS OR SYMPTOMS AT TIME OF DIAGNOSIS SINGLY OR IN COMBINATION	CHARACTER AND EXTENT OF LESION BY ROENTGENOGRAM*					
	Inactive		Questionably Active		Active	
	Number	Per cent	Number	Per cent	Number	Per cent
Total	204	100.0	301	100.0	87	100.0
No signs or symptoms	149	73.0	183	60.8	18	20.7
Fatigue	17	8.3	44	14.6	25	28.7
Cough	26	12.8	58	19.3	53	60.9
Hemoptysis	3	1.5	16	5.3	13	14.9
"Streaking"	4	2.0	4	1.3	6	6.9
Chest pain	11	5.4	42	14.0	18	20.7
Gastrointestinal symptoms	6	3.0	9	3.0	—	—
Pleurisy with effusion	—	—	4	1.3	2	2.3
Moist rales	1	0.5	11	3.7	22	25.3

* See Table 6.

In each classification a larger percentage of females than males began to "cure," and for both sexes a larger percentage began to "cure" at the younger ages than at the older ages.

Symptoms and physical signs at the time of diagnosis are shown in table 3. Among the males, signs and symptoms were more frequent at the younger ages, while among the females age does not seem to be an important factor. In the whole group about 60 per cent were asymptomatic. It is interesting to note that 20.7 per cent of the "active" cases and 60.8 per cent of the "questionably active" cases had no signs or symptoms. On the other hand, 3.5 per cent with lesions classified "inactive" had hemoptysis or "streaking," indicating the necessity for careful clinical study of all cases. Although fatigue and cough occur frequently among the tuberculous, it is not believed that their presence is necessarily of much

[4] "Cure" means cessation from work; treatment for tuberculosis, usually at the Company sanatorium at Mount McGregor.

importance in routine survey work. These complaints are encountered so frequently in nontuberculous employees that it is believed that their diagnostic significance is doubtful.

The incidence of overweight and underweight in the 592 was about the same as in our whole home office group.

Bilateral disease was found in 160 males and females but, since the experience of these persons proved to be similar to those in comparable groups whose lesions were unilateral but of the same extent, these cases are not differentiated in the tables.

As a fulfillment of the objective of the study, to discover an aid toward disposition and an indication of the future course and outcome, the recorded experience in relation to the "extent only" (minimal, moderately advanced, far advanced) of the disease at the time of detection was not particularly definitive. Performance was in general about what might have been expected. Those employees with advanced disease had a more serious health problem than those with minimal lesions. The advanced cases had more physical signs and symptoms, were advised more frequently to "cure," had a longer "cure" at the sanatorium, and had a higher mortality. "Extent " alone at the time of detection is not in itself of much help as an aid to disposition or medical recommendation.

But when the material is classified by a combination of *character* and *extent* of the disease, a more accurate prognosis can be made. It is true that some individuals in each group run a course contrary to the majority, but on an average the extent together with character of the lesion aid greatly in deciding the disposition of the case and indicate with surprising reliability the course and ultimate outcome. The length of "cure," the repetition of "cures," and the status on the first, fifth, tenth, and fifteenth anniversaries of diagnosis indicate markedly that the cases classified by roentgenogram as "inactive" had the lesser problem while the cases classified by roentgenogram as "active" had the most serious problem. The "questionably active" cases fell in between.

The length of cure at Mount McGregor was influenced by varying factors over the years. However, those with lesions classified as "inactive" "cured" the shortest time and none died; those with "questionably active" lesions "cured" longer and 2.9 per cent died; those with lesions classified as "active" had, on the average, the longest cures and 7.8 per cent died.

The experience in the first year of follow-up is depicted in figure 1. The definition of "satisfactory" means that the serial roentgenograms revealed stability or improvement of the lesion, significant signs or symptoms disappeared or were absent, and laboratory tests were negative. "Unsatisfactory" experience includes progression of the lesion as shown by serial roentgenograms, presence or development of significant signs or symptoms, or positive laboratory tests. Of those who began to "cure," about 80 per cent of the "inactive" cases had a satisfactory experience compared with a little over 50 per cent of the "questionably active" and about 25 per cent of the "active." Of those who continued at work, only 7.2 per cent of the "inactive" cases began to "cure" within a year compared with 33.3 per cent of the "questionably active" and 70.0 per cent of the "active." These were included in the group having "unsatisfactory" experience.

Of the 592 cases, 505 have been followed for five years or more, 377 for ten years or more, and 190 for fifteen years or more. Their status on their fifth, tenth, and fifteenth anniversaries of diagnosis and their interval history, divided by the character and extent of the lesion at the time of diagnosis, are shown in table 4.

It is interesting to note after fifteen years of follow-up that in the "inactive" group only 18.8 per cent had "cured" once, 10.9 per cent had relapses and none had died of tuberculosis. In contrast, in the "questionably active" group 45 per

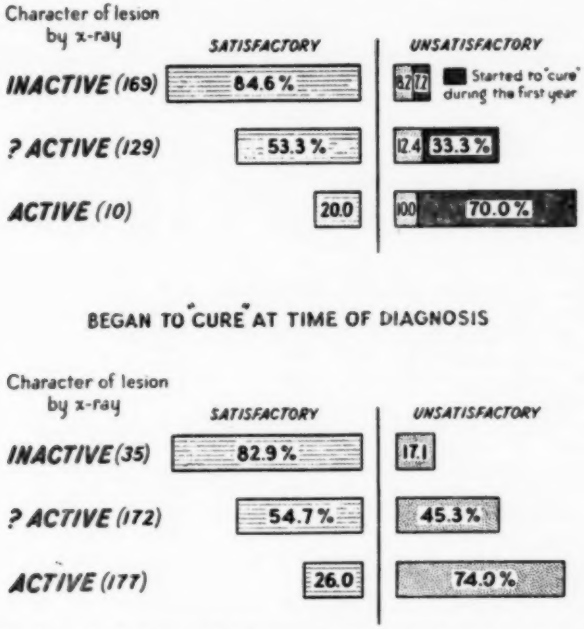

FIG. 1. Experience in first year of follow-up. Continued at work at time of diagnosis under medical supervision.

cent "cured" once, 18.7 per cent had relapses in fifteen years, and 7.7 per cent died of tuberculosis; and in the "active" group all "cured" and 17.1 per cent had died of tuberculosis. The percentage of multiple "cures" in the "active" group was only 14.3. This apparently low figure was influenced by some very long first "cures" and by the high percentage of deaths.

The experience of the "inactive" group was distinctly more favorable than that of the "questionably active" group, and that in turn was more favorable than that of the "active" group. On the fifth, tenth, and fifteenth anniversaries of diagnosis, about three-quarters of the "inactive" group had worked continuously as compared with one-quarter of the "questionably active" group, and only one per cent of the "active" group. In general the experience for the males

in each group and at each anniversary was better than for the females, and the experience for the older groups was better than for the younger groups for both sexes.

However, the experience of persons over age 40 with "inactive" lesions calls for special comment. In the early years of the program of continual observation, persons over age 40 with apparently healed lesions were given a roentgenographic examination every three years. It was noticed, however, that it was not uncommon to find unstable lesions in this older group after years of stability. In those days it was more usual to look for active tuberculosis in the younger group

TABLE 4

Status and Interval History at Fifth, Tenth, and Fifteenth Anniversaries of Diagnosis According to Character of Lesion by Roentgenogram at Diagnosis

ANNIVERSARY	TOTAL		AT WORK						CURING				DECEASED (TUBERCULOSIS)	
Character and Extent of Lesion by Roentgenogram at Diagnosis*			Has worked continuously		Has cured once		Has cured twice or more		First cure		Subsequent cure			
	Number	Per cent	Number	Per cent	Number	Per cent	Number	Per cent	Number	Per cent	Number	Per cent	Number	Per cent
5th Anniversary														
Inactive	171	100.0	124	72.5	37	21.7	5	2.9	1	0.6	4	2.3	—	—
Questionably active	255	100.0	62	24.3	143	56.0	7	2.8	22	8.6	14	5.5	7	2.8
Active	79	100.0	1	1.3	53	67.1	2	2.5	14	17.7	3	3.8	6	7.6
10th Anniversary														
Inactive	129	100.0	93	72.1	25	19.4	7	5.4	1	0.8	3	2.3	—	—
Questionably active	182	100.0	44	24.2	101	55.5	18	9.9	1	0.4	9	5.0	9	5.0
Active	66	100.0	1	1.5	49	74.3	2	3.0	2	3.0	3	4.6	9	13.6
15th Anniversary														
Inactive	64	100.0	45	70.3	12	18.8	5	7.8	—	—	2	3.1	—	—
Questionably active	91	100.0	26	28.6	41	45.0	16	17.6	—	—	1	1.1	7	7.7
Active	35	100.0	—	—	24	68.6	2	5.7	—	—	3	8.6	6	17.1

* See Table 6.

although the U. S. Census statistics indicated that the death rate was highest for males at the older ages and for females at the younger ages. Although the group is small (table 5), the experience indicates clearly that "inactive," or apparently arrested tuberculosis, should not be "forgotten" among older people and the necessity for continued periodic re-examination of all persons with lesions characteristic of tuberculosis should be emphasized.

Besides the experience with the home office employees another objective check is available on the efficacy of this classification and disposition. Since 1930 a decision has been made on 746 chest roentgenograms submitted by applicants for life insurance. Those showing lesions were divided into two groups roentgeno-

logically, "active" and "inactive" tuberculosis. Since the groups were comparable in age distribution, the same percentage of deaths might have been expected in each group except for the chest condition as disclosed by the roentgenographic examination. It was found, however, that in the group of 178 classified by roentgenogram as "active" cases, 10.7 per cent had died of tuberculosis within nine years compared to 0.4 per cent in the group of 568 classified as "inactive" cases. The number of deaths from tuberculosis expected among white males of the United States of comparable age (1931–1940) was 0.7 per cent. These results have been published in detail elsewhere (3, 4).

This opportunity with its wide scope and years of follow-up among employees and applicants for life insurance has revealed many aspects of the tuberculosis problem not seen generally by phthisiologists. After analyzing the results of this

TABLE 5

Trends of Serial Roentgenograms during Five-Year Periods
Employees who had never cured for Tuberculosis

SEX AGE	TOTAL	LESION STABLE	LESION BECOMING CALCIFIED	LESION UNSTABLE OR PROGRESSIVE
Males				
40 to 44	22	18	1	3
45 to 49	42	32	4	6
50 to 54	48	42	2	4
55 to 59	36	35	—	1
60 to 64	26	18	1	7
Females				
40 to 44	16	15	1	—
45 to 49	17	16	—	1
50 to 54	15	15	—	—
55 to 59	13	9	—	4

carefully planned long range follow-up it is believed that it is possible to adopt a practical program of classification and disposition based upon the original roentgenographic examination. A satisfactory tuberculosis detection and control program may be instituted with safety for the individual patient if he is followed up carefully and advantageously for the community which can plan to use available treatment facilities.

The roentgenographic classification and suggested medical recommendation is shown in table 6.

DISCUSSION

When a person with an abnormal chest roentgenogram is detected in a routine case-finding survey, a recommendation and disposition must be made. In the majority of instances, conclusive clinical and laboratory evidence will be lacking to assist in this step. In the writers' experience a technically satisfactory roentgenogram (in this report "roentgenogram" means a technically satisfac-

TABLE 6

Roentgenographic Classification and Medical Recommendation

CLASSIFICATION OF LESION BY ROENTGENOGRAM	ROENTGENOGRAPHIC APPEARANCE	RECOMMENDATION	MEDICAL ACTION
Inactive	Extent: Any minimal or borderline moderately advanced. (N.T.A.) Character: Fine or coarse strands; small or large calcific densities, small opaque areas with borders clearly outlined. May be localized or scattered.	Continue at work.	Careful supervision and periodic roentgenographic examination throughout life.
Questionably active	A. Extent: Extensive minimal or any moderately advanced. (N.T.A.) Character: Areas have general characteristics described above but tending toward "softness." B. Extent: Any minimal or borderline moderately advanced. (N.T.A.) Character: Areas of cloudy mottling or homogeneous densities; borders hazy or not clearly defined; no suggestion of cavity.	Observation as soon as possible, preferably in a sanatorium for about three months.	1. Careful study including serial roentgenograms and repeated sputum examinations. 2. Instruction in treatment and control of tuberculosis. 3. Individual without evidence of active tuberculosis may return to work under careful supervision and periodic roentgenographic examination throughout life. 4. Individual with evidence of active tuberculosis to complete "cure."
Active	A. Extent: Far advanced. (N.T.A.) B. Extent: Moderately advanced. (N.T.A.) Character: Characteristics as II-B; total cavitation must be less than 4 cm. C. New lesion: Any shadow regardless of extent or character developing subsequent to a roentgenogram interpreted as "normal" or "average."	Admit to hospital or sanatorium immediately.	Treat as active tuberculosis and as circumstances indicate.

tory 14 by 17 celluloid film), interpreted in accordance with the classification as described, can be used as a basis for preliminary disposition. Further study and observation will modify or confirm the accuracy of the original decision. But it should be emphasized that there are distinct limitations to the use of roentgenography as follows:

A tuberculous lesion may be present and not visible on the film.
A cavity may be present but not visible.
"Hard" lesions may contain areas of definite activity.
A tuberculous lesion may have healed without visible scar.
Small lesions may be overlooked even by experienced radiologists.
Group behavior can be forecast accurately, but there will be individual exceptions.
Judgment and experience in interpretation are variable at present among physicians.

Nevertheless, it is believed that the roentgenogram offers the best single bit of evidence in evaluating a case.

The experience of the roentgenologically "active" and "inactive" groups emphasizes the different behaviors of the extremes. Inevitably there is a "questionably active" group of cases which have about an even chance of becoming frankly "active" or proving to be "inactive." Whether it is better to treat this intermediate group as active tuberculosis is an open question concerning which opinions vary. The writers believe that the proposed plan of a relatively short period of education and intensive study, during which a more accurate estimation of the best procedure to follow can be made, offers a satisfactory solution.

As a result of the observations and experience in the present study, the writers have one unshaken conviction and that is that all cases with lesions which may be of tuberculous origin should have medical observation and periodic roentgenographic examinations throughout life.

SUMMARY

1. A technically satisfactory roentgenogram of the chest made in a routine case-finding survey can be classified so as to make a reasonably accurate preliminary disposition and long-range prognosis.

2. All persons whose roentgenograms disclose pulmonary involvement which may be tuberculous in character should have medical supervision throughout life.

SUMARIO Y CONCLUSIONES

Tuberculosis: Estudio de la Disposición y Observación Subsiguiente a Base de la Naturaleza y Extensión de la Lesión Observada en la Radiografía Inicial

Una radiografía técnicamente satisfactoria del tórax, obtenida en una encuesta colectiva corriente en busca de casos, puede ser clasificada de modo que permita hacer con bastante exactitud una disposición preliminar del caso y un pronóstico a largo plazo.

Todas las personas cuyas radiografías revelen afección pulmonar que pueda ser de naturaleza tuberculosa deben continuar bajo vigilancia médica toda su vida.

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MINIATURE CHEST ROENTGENOGRAMS IN SCHOOLS AND INDUSTRIES IN SAN ANTONIO, TEXAS

P. A. PAMPLONA[1] AND W. F. HAMILTON

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INTRODUCTION

As part of the tuberculosis program, the Tuberculosis Control Division of the San Antonio City Health Department started a roentgenographic survey in the schools and industries located in the city. At the time the survey was started, the photofluorographic unit promised by the Texas State Department of Health was not available. Major Herman S. Wigodsky, Director of Research at the AAF School of Aviation Medicine at Randolph Field, aware of the work of the City Health Department, offered a 35 mm. mobile photofluorographic unit to the Tuberculosis Division for the purpose of carrying on the survey. All of the equipment and personnel to operate this unit were kindly furnished by the Air University, School of Aviation Medicine under the command of Col. H. G. Armstrong, M. C.

The mobile unit was created as one of the many improvements by the USSTAF in England during World War II. Wayburn's study of the AAF personnel surveyed by this unit in England, from April to September 1945, is a very interesting one and brings up the importance of mass roentgenographic surveys. Of the 77,016 persons examined, only 0.36 per cent had evidence of reinfection tuberculosis (13). This low incidence was to be expected, since the author was dealing with a particular type of population which had been screened at the time of induction. Most of the suspected and definite cases of tuberculosis had been previously eliminated from the ranks. Considering the number of months in the service (varying from twelve to fifty-five months or more), the mental and physical stress of soldiers in combat, and the not always ideal living conditions brought about by the war, the prevalence of tuberculosis in this group remained very low. The low percentage found in this study indicates that by intensive case finding and other tuberculosis control measures it is possible to maintain a low morbidity rate even when people are living under strenuous conditions.

In September 1945, the unit was sent back to the United States to be stationed at Randolph Field. Operating the unit during this summer was a team of six Army men, including the medical officer in charge. The medical officer, besides controlling the work of the unit, interpreted the films in collaboration with the Chief of the Tuberculosis Control Division of the City Health Department.

Prior to the examination of the several interested groups, the Bexar County Tuberculosis Association and the City Health Department carried out a preparatory health education program in order to inform such groups of the need for, and the advantages of, a chest roentgenographic survey. The Tuberculosis

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Association distributed literature, posters, and showed motion pictures. Educational talks were given by the Chief of the Tuberculosis Control Division and the Tuberculosis Association Health Educator.

In San Antonio the population is composed of three different racial groups: Group A[2], Group B[3], and Group C[4]. This racial grouping will be observed throughout the discussions in this paper. It is important to maintain this classification because of the prevalence of tuberculosis existing in Group B in this area (6, 10). The underprivileged socio-economic conditions under which Group B lives in this part of the country probably has an important influence on the prevalence of tuberculosis. In Mexico, according to Yelton (14), the tuberculosis death rate per 100,000 population was 56 as compared to 47 in the United States, a not very significant difference.

The results in this survey are based primarily on roentgenographic interpretations, therefore, subject to change after a more accurate and detailed study of the cases detected. All individuals found to have any chest involvement were referred to their private physician or to the City Chest Clinic for further study, care, and follow-up.

RESULTS

For purposes of discussion, the results of the survey will be divided into two groups: Schools and Industries.

Schools

Table 1 gives a general and detailed picture of the findings among the students examined. The percentages given include all persons examined roentgenographically in the schools, that is, students, teachers, clerical staff, and other personnel, and also some parents and relatives in one of the schools. Eight thousand, nine hundred eighty-three persons were examined, of which 54.1 per cent belonged to Group A, 36.7 per cent to Group B, and 9.2 per cent to Group C. Eleven Chinese and one Japanese were included in this last group (table 1).

Of the 8,983 persons examined, 43, or 0.48 per cent, showed evidence of reinfection tuberculosis. By breaking down the total number of persons examined into racial groups, it is observed that of the 4,864 of Group A examined, 14, or 0.29 per cent, showed evidence of reinfection tuberculosis; of the 3,291 of Group B examined, 27, or 0.82 per cent, had evidence of reinfection tuberculosis; and, finally, of the 828 of Group C examined, 2, or 0.24 per cent, had roentgenographic evidence of reinfection type tuberculosis.

It is of interest to observe that Group B showed a higher percentage of tuberculosis than Group A. The low percentage among Group C may be attributed to the small number examined roentgenographically and also to their much better standard of living in this part of the country, while the opposite is true of Group B. These facts may distort the true picture of tuberculosis prevalence among

[2] White, excluding Mexican Nationals and those of Mexican descent.
[3] White Mexican Nationals and those of Mexican descent.
[4] Negro.

TABLE 1

Schools

Number of Persons Examined and Number and Per cent with Reinfection Tuberculosis by Race, Sex and Age, San Antonio, Texas, 1947

AGE	RACE																			
	Group A						Group B						Group C						Total reinfection TB	
	Sex																			
	Males			Females			Males			Females			Males			Females				
	Number examined	Number TB	Per cent	Number examined	Number TB	Per cent	Number examined	Number TB	Per cent	Number examined	Number TB	Per cent	Number examined	Number TB	Per cent	Number examined	Number TB	Per cent	Number Examined	Number TB	Per cent
0 to 4	0	0		2	0		2	0		0	0		0	0		0	0		4	0	
5 to 9	17	0		13	0		15	0		10	0		0	0		0	0		55	0	
10 to 14	455	0		434	3	.69	244	2	.82	298	2	.67	46	0		47	0		1,524	7	.46
15 to 19	1,749	6	.34	1,606	2	.12	1,220	5	.41	1,290	15	1.16	243*	1	.41	293‡	1	.34	6,401	30	.47
20 to 24	116	0		64	0		73	0		22	0		64†	0		10	0		349	0	
25 to 29	29	0		37	0		13	0		17	0		49	0		6	0		151	0	
30 to 39	25	0		99	0		4	0		28	2	7.14	28	0		17	0		201	2	1.0
40 to 49	33	1	3.0	94	0		6	0		20	0		9	0		6	0		168	1	0.6
50 to 59	11	2	18.2	38	0		5	0		6	0		2	0		4	0		66	2	3.0
60 and over	8	0		5	0		3	0		5	1	20.0	0	0		0	0		21	1	4.8
Unknown	3	0		26	0		5	0		5	0		1	0		3	0		43	0	
Total.....	2,446	9	.37	2,418	5	.21	1,590	7	.44	1,701	20	1.18	442	1	.23	386	1	.26	8,983	43	.48

* 4 Chinese, 1 Japanese.

† 3 Chinese.

‡ 4 Chinese.

them. According to Picnot, the annual family income most prevalent among Group B was $622.34; Group C, $937.50; and Group A, $949.02. The most prevalent individual incomes of these three respective groups were: Group B, $141.44, Group A, $256.49 and Group C, $284.09 (7).

Comparing the percentages found by race and sex, the only striking difference is observed among the females in Group B where 1.18 per cent had roentgenographic findings of reinfection tuberculosis. Similar findings are observed in the age group 15 to 19 where 1.16 per cent showed evidence of tuberculosis, while for the other racial groups and sexes the percentages remained under one.

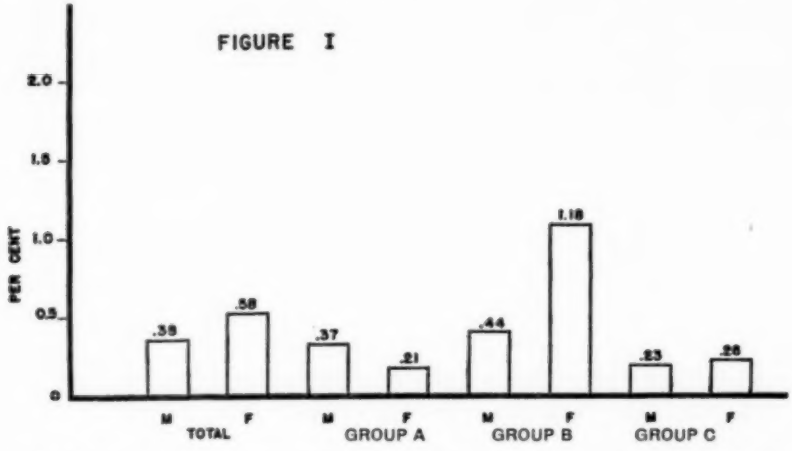

FIG. 1. Per cent reinfection tuberculosis among students, by race and sex, in San Antonio, Texas, 1947.

It is of interest to break down table 1 and obtain the percentages in the age groups 10 to 24, which include most of the high school and college students. Another reason for choosing this age group is that in San Antonio tuberculosis prevails in the age group 10 to 39, as can be seen in the following chart (figure 2).

In table 2 it is seen that among the total of Group A (4,424) examined in age group 10 to 24, 11, or 0.25 per cent, had evidence of reinfection tuberculosis; of the 3,147 of Group B, 22, or 0.76 per cent, had evidence of the disease; and, finally, of the 703 of Group C, 2, or 0.28 per cent, showed evidence of reinfection tuberculosis. Of the total number of persons examined in this age group (8,274), 37, or 0.45 per cent, showed evidence of tuberculosis. As can be observed, the total percentages differed slightly; 0.48 per cent for the total group examined and 0.45 per cent for the age group 10 to 24. Differences are more noticeable when taking the racial groups individually, either as a total or by the age group in question, in either of which Group B reveals a higher percentage than the other two groups examined.

In spite of the limited number of roentgenograms taken among the schools in San Antonio and Bexar County, these findings are very similar to those observed in other states. Edwards in New York found the percentage of clinically

FIGURE 2
DEATHS

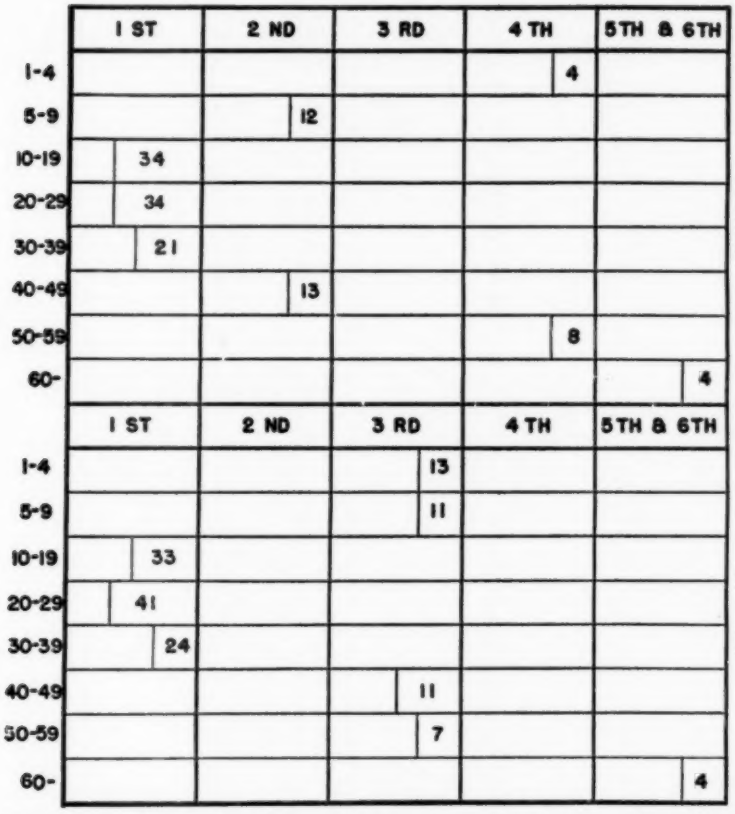

FIG. 2. Per cent and rank of tuberculosis as a cause of death in two selected five year periods of time, in San Antonio, Texas, 1926–1930 and 1941–1945.

significant tuberculosis to be 0.2 in 16,000 college students (8). According to a publication of the United States Public Health Service (12), school surveys conducted in various states showed only slight fluctuation in the results. In Michigan, for example, 2,788 students were examined roentgenographically and 0.3 per cent were found to have reinfection tuberculosis. In Alabama, 7,770 students were examined and showed evidence (0.4 per cent) of tuberculosis. Similar studies

TABLE 2

Schools

Number of Persons Examined and Number and Percentage of Reinfection Tuberculosis in the Age Group 10 to 24 by Race and Sex, San Antonio, Texas, 1947

AGE	RACE																			
	Group A						Group B						Group C						Total reinfection tuberculosis		
	Sex																			
	Males			Females			Males			Females			Males			Females					
	Number examined	Number TB	Per cent	Number examined	Number TB	Per cent	Number examined	Number TB	Per cent	Number examined	Number TB	Per cent	Number examined	Number TB	Per cent	Number examined	Number TB	Per cent	X-ray	Number TB	Per cent
10 to 24	2,320	6	.26	2,104	5	.24	1,537	7	.46	1,610	17	1.1	353	1	.28	350	1	.29	8,274	37	.45

in Florida (13,000 students), New York (16,128), and District of Columbia (3,084) showed percentages between 0.5 and 0.7 per cent. In contrast, in San Antonio and Bexar County, 0.48 per cent of students with reinfection type tuberculosis were found among 8,983 examined. Considering all states surveyed, 81,529 chest roentgenograms were made and of these 452 had evidence of reinfection pulmonary tuberculosis, thus giving a percentage of 0.6 per cent. In

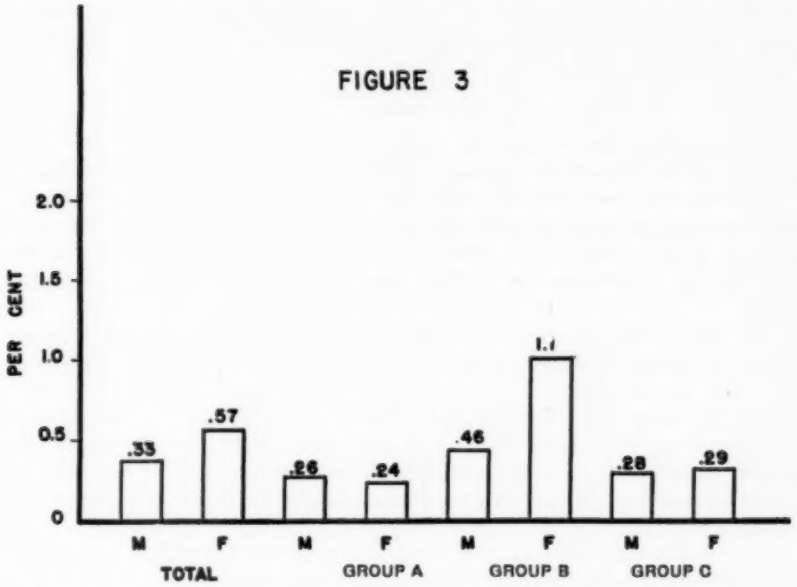

FIG. 3. Per cent reinfection tuberculosis among students in age group 10 to 24 by race and sex in San Antonio, Texas, 1947.

TABLE 3

Nontuberculous Pathology among Students Examined in San Antonio, Texas, in 1947

Bone disease	13	Diagnosis reserved	3
Cardiovascular	6	Bronchiectasis	2
Pleural abnormalities	4	Tumor masses	1

the Public Health Service study, as well as in the present one, the same class of persons was included, that is, students, teachers, and maintenance personnel of high schools and colleges.

An interesting survey was made by R. Tak Eng in Hong Kong, China, in 1940–1941, prior to Japanese occupation. Eng reports that 4,644 students were fluoroscoped and that 124, or 2.3 per cent, had pulmonary tuberculosis. This

incidence is very high, but, as remarked by the author, "... the population of Hong Kong had increased to three times its normal in the three years preceding our survey. Refugees had flocked in from various parts of China, making proper housing, nutrition and sanitation difficult" (2). Again, the importance and influence of the socio-economic status stands out in the picture of tuberculosis prevalence.

Of incidental interest is the presence of chest disease other than tuberculosis, which was found in 0.32 per cent of the total persons examined. The predominating age group for nontuberculous pathology was 15 to 19, with 21 of the 29 persons found falling into this group.

Industries

In the eighteen industrial groups examined, workers for the Community Chest service and from one of the insurance companies of San Antonio were included; also 266 ranchers and stockyard employees not directly associated with industry. The remaining groups were employed by industrial plants in the city. The total number of the nonindustrial workers examined roentgenographically was not large enough to influence the findings; they were, therefore, kept in the total group.

The high percentage of tuberculosis found in industry has caused a debate among all authors studying roentgenographic surveys of industrial workers. Is it true that the prevalence of tuberculosis is higher among industrial workers or should the known fact that a higher incidence exists among unskilled workers be taken into consideration? Goldberg says: "The death rate among the unskilled worker is more than twice that of the skilled worker." He continues, "Limited earning capacity has a direct relationship to tuberculosis in industry" (3).

A more thorough investigation should be made to ascertain the true value of these findings among industrial workers. The importance of the socio-economic status of the groups examined must always be borne in mind because this will definitely influence the prevalence of the disease. This fact cannot be overlooked in San Antonio where 40 per cent of the total population falls within Group B with very limited earning capacity (6, 10).

Martin, Pessar, and Goldberg (3) found 2.3 per cent of clinical tuberculosis among food-handlers. In San Antonio, in a study of 17,790 food-handlers examined roentgenographically at the City Health Department, a percentage of 3.3 was found, of which 1.8 per cent were suspects and 1.5 per cent definite (6). Merriweather, Sayers, and Lanza (3) reported 2.4 per cent and 2.6 per cent, respectively, for the years 1928 and 1929 in lead and zinc miners of Oklahoma, Kansas, and Missouri. The presence of silicosis may be responsible for this high percentage, since diagnosis was established by roentgenographic findings alone. A report of the U. S. Public Health Service of surveys in industry for the years 1942 to 1946 revealed a percentage of 1.1 for this country (11). Hilleboe, reporting on roentgenograms taken among industrial workers throughout the country in 1942 to 1944 gives the figure 1.5 per cent for the prevalence of reinfection

TABLE 4

Industries

Number of Persons Examined and Number and Per cent with Reinfection Tuberculosis by Race, Sex and Age, San Antonio, Texas, 1947

AGE	RACE																		Total reinfection tuberculosis		
	Group A						Group B						Group C								
	Sex																				
	Males			Females			Males			Females			Males			Females					
	Number examined	Number TB	Per cent	Number examined	Number TB	Per cent	Number examined	Number TB	Per cent	Number examined	Number TB	Per cent	Number examined	Number TB	Per cent	Number examined	Number TB	Per cent	Number examined	Number TB	Per cent
10 to 19	42	0		59	0		49	0		43	1	2.3	7	0		2	0		202	1	0.5
20 to 29	258	4	1.5	150	0		250	10	4.0	208	2	0.96	30	0		35	0		931	16	1.7
30 to 39	295	10	3.4	110	1	0.9	208	6	2.8	114	4	3.5	48	1	2.1	21	0		796	22	2.8
40 to 49	256	5	2.0	114	4	2.8	128	4	3.1	53	0		38	3	7.9	9	1	11.1	628	17	2.7
50 to 59	141	3	2.1	46	1	2.1	79	4	5.0	18	1	5.5	8	0		1	0		293	9	3.1
60 to 69	56	1	1.8	12	0		28	0		3	2	66.0	9	0		0	0		108	3	2.8
Unknown	42	0		49	0		25	3	12.0	58	2	3.4	0	0		0	0		174	5	2.9
Total.....	1,090	23	2.1	570	6	1.15	767	27	3.5	497	12	2.4	140	4	3.6	68	1	1.5	3,137	73	2.3

FIGURE 4

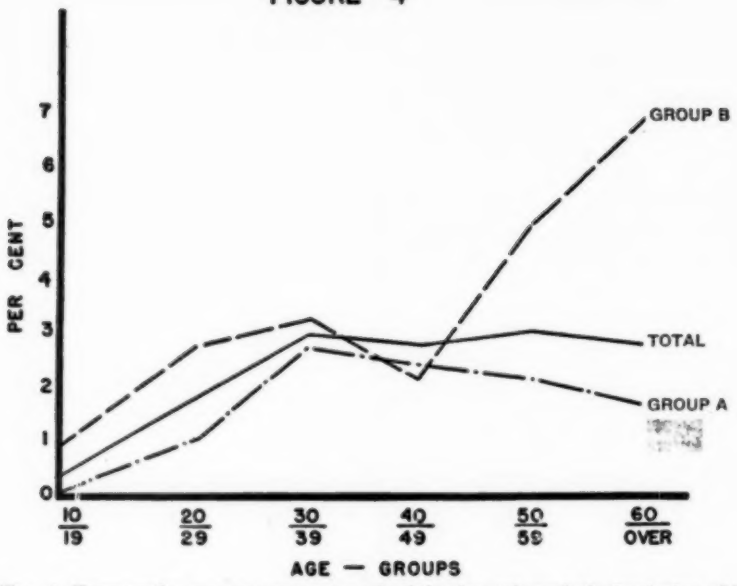

FIG. 4. Comparative percentage curves of reinfection tuberculosis (exclusive of local Negroes) among industrial workers, by race and age, San Antonio, Texas.

FIGURE 5

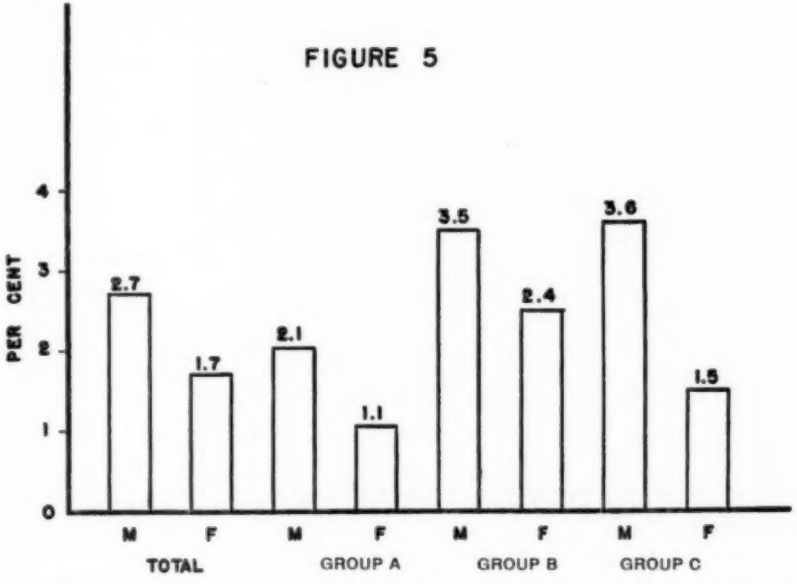

FIG. 5. Per cent reinfection tuberculosis among industrial workers, by race and sex, in San Antonio, Texas, 1947.

tuberculosis among these adults (5). Elkin, Irwin, and Kurtzhalz in Philadelphia in 1942 examined 71,767 industrial workers and found 2.3 per cent with evidence of reinfection tuberculosis, based solely on the interpretation of the survey films (1). The same figure, 2.3 per cent reinfection tuberculosis, was observed in this survey made in San Antonio in which 3,132 roentgenograms were obtained and 73 persons had reinfection type tuberculosis. The findings by age groups, race, and sex are presented in table 4.

Fifty-three per cent of the total individuals examined were in Group A, 40.4 per cent belonged to Group B, and 6.6 per cent to Group C. This percentage distribution is similar to the one observed among the schools and also to the city's population percentage distribution which is composed of 53 per cent in Group A, 40 per cent in Group B, and 7 per cent in Group C (6). Since the same percentage distribution holds true in the industrial sample as it does in the city's population, this sample should give a fairly accurate picture of the prevalence of tuberculosis in the San Antonio industrial groups examined.

Of the 3,132 persons examined, 73, or 2.3 per cent, had roentgenographic evidence of reinfection tuberculosis. Dividing the total number examined into racial groups: 1,660 in Group A were examined, of whom 28, or 1.7 per cent,

TABLE 5

Nontuberculous Pathology Among Industrial Workers Examined in San Antonio, Texas, in 1947

Cardiovascular	10	Pneumoconiosis	3
Bone disease	5	Tumor masses	2
Pleural abnormalities	4	Diagnosis reserved	2
Bronchiectasis	3	Fibrosis	1

showed evidence of the disease; of the 1,264 in Group B examined, 39, or 3.1 per cent, had findings of tuberculosis; and of the 208 in Group C, 5, or 2.4 per cent, had roentgenographic evidence of tuberculosis of the reinfection type.

The total reinfection tuberculosis percentage curve rose from 0.5 per cent in the age group 10 to 19 to 3.1 per cent in the age group 50 to 59. This percentage curve rises progressively to a peak in the older age groups, as is observed in the usual tuberculosis morbidity curves. Of importance was the difference in the racial groups, where those in Group B have a curve which stands higher throughout the different age groups with a drop in the 40 to 49 age groups and a second rise in the age groups 50 and over. This may be seen in figure 4.

The findings for those in Group C have not been placed in figure 4 because only two age groups were represented with very high incidence, causing a false representation of the prevalence of tuberculosis among them.

Also of interest were the 30 cases (0.95 per cent) of nontuberculous disease of the chest found among the 3,132 persons examined. Examining these 30 cases by age, it is observed that the majority of the cases is in the age groups above 40 with the highest number in the age group 50 to 59. These persons were referred to their private physicians and to the city chest clinic for further investigation and follow-up.

SUMMARY

The roentgenographic findings in a chest survey of 12,115 students and industrial workers in the city of San Antonio, Texas, are as follows:

A total of 8,982 students were examined and 43, or 0.4 per cent, showed evidence of reinfection tuberculosis. Of the total, 4,864 were in Group A[2], of whom 14, or 0.29 per cent, showed roentgenographic evidence of tuberculosis; 3,291 were in Group B[3], with 27, or 0.82 per cent, having pulmonary reinfection type tuberculosis; and 828 were in Group C[4], of whom 2, or 0.24 per cent, had roentgenographic evidence of the disease.

A total of 3,132 industrial workers were examined and 73, or 2.3 per cent, had evidence of reinfection tuberculosis. Of the total, 1,660 were in Group A, of whom 29, or 1.7 per cent, had evidence of pulmonary tuberculosis; 1,264 were in Group B with 39, or 3.1 per cent, with evidence of reinfection tuberculosis; and 208 were in Group C, of whom 5, or 1.5 per cent, showed evidence of reinfection pulmonary tuberculosis.

In this study the prevalence of tuberculosis among those in Group B is higher throughout all age groups, either in the schools or the industrial workers examined.

Emphasis was placed on the socio-economic status of those in Group B and its relationship to the prevalence of tuberculosis among them in this part of the country.

In this survey, other abnormalities of the chest were found in 0.32 per cent of the students, with bone involvement as the primary finding. Of the industrial workers examined roentgenographically, cardiovascular abnormalities prevailed among the 0.95 per cent of the nontuberculous chest findings.

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Case Reports

MILIARY TUBERCULOSIS CAUSED BY INTRAVENOUS SELF-INJECTION OF TUBERCLE BACILLI, TREATED SUCCESSFULLY WITH STREPTOMYCIN THERAPY[1]

OSWALD R. JONES, WARREN D. PLATT, AND LUIS A. AMILL

(Received for publication May 27, 1949)

A case of miliary tuberculosis caused by the intravenous injection of a massive dose of virulent tubercle bacilli gives the clinician a rare opportunity to study this disease under ideal circumstances for investigation. The following is a case study of a 30-year-old unmarried female, an experienced bacteriologist, who injected herself intravenously with 1.0 cc. of suspension of virulent strain of tubercle bacilli with possible suicidal intent. The injection was made into the left antecubital vein. She stated that she prepared the inoculum by washing a few cc. of saline over a slant of Petragnani's medium which contained a 14-day growth of *M. tuberculosis*. The culture represented a primary isolation from the pleural fluid of a young man with an acute tuberculous pleurisy. An interesting background to this episode is the fact that three years previously, while inoculating a guinea pig, she had accidentally punctured the skin of her left antecubital fossa with a needle contaminated with tubercle bacilli. Following this, she noticed a very small superficial papule at the puncture site which disappeared after a few weeks and was not associated with further swelling, induration, tenderness, or any systemic symptoms. Previous to this episode in 1945, she does not remember having had a tuberculin skin test. One year after the 1945 incident, however, a tuberculin skin test was positive.

The patient (L. F.) was admitted to St. Luke's Hospital on January 15, 1948, the day following the intravenous injection, but did not reveal any information concerning her self-inoculation. Instead, she complained of a five-pound weight loss, night sweats, fatigue, urinary frequency, "pus in her urine," and a chronic nonproductive cough of three months duration. She emphasized the fact that she had worked in a Veterans Hospital for tuberculosis in 1945.

The patient was referred to the urology service with a tentative diagnosis of pyelonephritis, possibly tuberculous in origin. Her temperature at the time of admission was 101.8° F., which subsided to normal on her second hospital day. The patient later stated that her temperature had gone to 104°F. a few hours after the injection and was on the way down (101.8°F.) when she was admitted to the hospital. She remained in the hospital for eight days during which she continued to be afebrile and asymptomatic except for the first day. Her blood count, routine urine examinations, urea nitrogen, and erythrocyte sedimentation rate were all within normal limits. A chest roentgenogram showed no abnormal densities in her lungs. Cystoscopy revealed the findings of a subsiding infection in the bladder. Pyelography showed pyelectasis and some clubbing of the calyses of the left kidney. Cultures (Petragnani's medium) of the urine of the bladder and both ureters, however, revealed no tubercle bacilli. A guinea pig inoculated with a twenty-four hour urine specimen taken at this time revealed no evidence of tuberculosis on subsequent examination.

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At the time of this admission, there was no mention of a lesion in the left antecubital fossa, but the patient later stated that on the day following her injection she had noticed swelling, redness, and tenderness at the injection site. She had squeezed a small amount of serum from the lesion and had seen tubercle bacilli in a smear of this material.

After eight days of study, the patient was discharged. On the following day, nine days after the injection, she again began to have severe chills and fever. She was readmitted on the fifteenth day after the injection with a temperature of 104°F. At this time she admitted for the first time that she had injected herself with tubercle bacilli. Considerable skepticism met this confession, however, and therapy was delayed for six days until a more positive diagnosis could be made. Physical examination was essentially negative except for a small, one mm. raised, slightly tender area in the left antecubital fossa (figure 1). There was no enlargement of the left epitrochlear or axillary lymph nodes. The total erythrocyte and leukocyte counts and examinations of the urine revealed no abnormalities. Serum agglutination reactions for typhoid, paratyphoid, brucellosis, and typhus were negative and no malarial parasites were seen on examination of the blood. The erythrocyte sedimentation rate was 56 mm. in one hour.

A chest roentgenogram obtained January 31, 1948 (figure 2) revealed no abnormalities after six days of a bounding fever with daily spikes up to 104°F. Streptomycin therapy

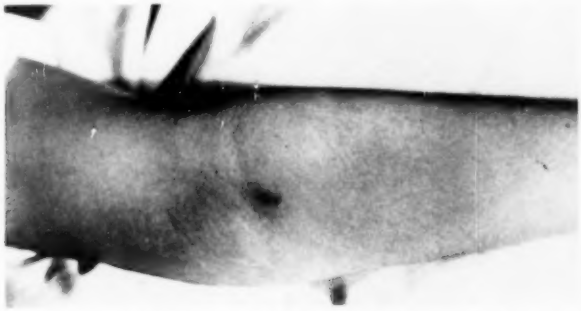

FIG. 1. Tuberculous lesion at the side of venipuncture in left arm.

(3.0 Gm. daily by the intramuscular route) was instituted because of the appearance of a generalized miliary infiltration throughout both lungs, as shown in chest films taken February 4, 1948 (figure 3). The infiltration had appeared at some time between the sixteenth and twenty-first days after the inoculation with tubercle bacilli. At this time (February 4) large numbers of acid-fast bacilli were seen on examination of a smear prepared from a small amount of serum expressed from the lesion in the left antecubital fossa. Cultures (Dubos, Petragnani) of this material were subsequently positive for *M. tuberculosis*. A tuberculin skin test with 1:100,000 dilution O.T., performed on February 5, was negative after forty-eight hours' observation.

Repeated blood cultures on both Petragnani and Dubos medium obtained after the start of streptomycin therapy were sterile. Moreover, subsequent guinea pig inoculation of the patient's blood, urine, and cerebrospinal fluid yielded negative results. The cerebrospinal fluid sugar, protein, chlorides, gold curve, and microscopic examination remained normal throughout the patient's hospital stay. Frequent microscopic examinations of the urine over a period of three months showed no abnormalities. The total leukocyte and differential counts remained within normal limits, whereas the patient showed a mild hypochromic, microcytic anemia one month after the beginning of her illness. This was subsequently corrected with the help of one 500 cc. whole blood transfusion, the administration of iron sulfate, and control of her infection.

The only areas manifestly affected by this massive injection of tubercle bacilli were the site of the injection and the lungs. The tip of the spleen was barely palpable on one occasion eight days after admission to the hospital during the height of the fever. Subsequent examinations, however, revealed no consistently demonstrable splenic enlargement. The ocular fundi showed no abnormalities at any time. Sputum examinations for tubercle bacilli were

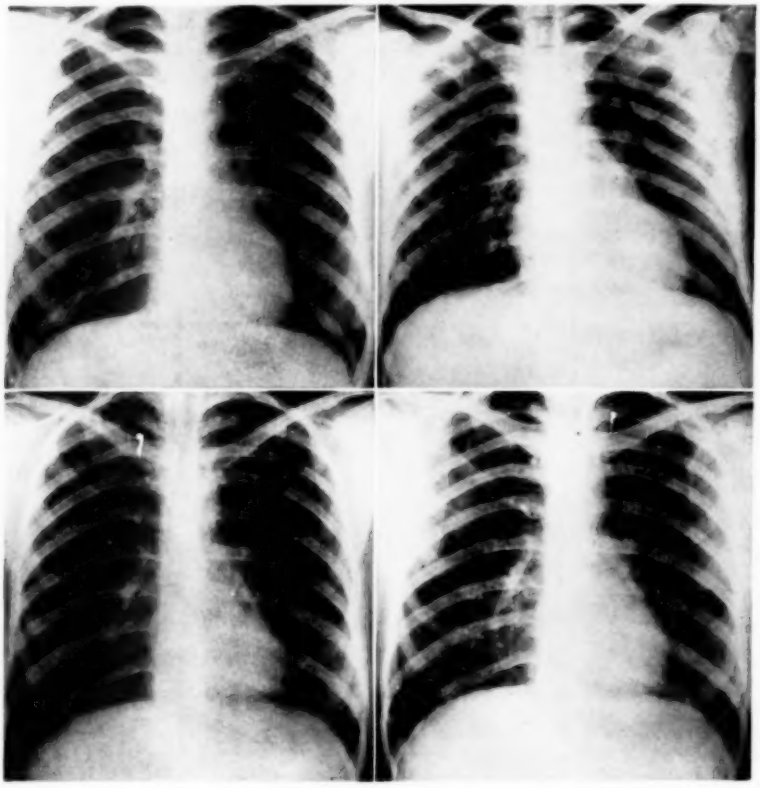

FIG. 2. (Upper left) Chest roentgenogram (January 31, 1948) obtained sixteen days after infection. No abnormalities are present.

FIG. 3. (Upper right) Chest roentgenogram (February 4, 1948) revealing miliary dissemination 20 days after infection.

FIG. 4. (Lower left) Chest roentgenogram (February 19, 1948). Miliary lesions are still well defined 36 days after infection.

FIG. 5. (Lower right) Chest roentgenogram (March 6, 1948). Miliary lesions seem to be more sharply outlined 51 days after infection.

negative on two occasions. A tuberculin skin test, 1:10,000, was positive after forty-eight hours on the twenty-sixth day after the inoculation. No significance was attached to this positive reaction because of the history of a previously positive tuberculin skin test in 1946.

It is probable that the immunity provided by the infection prior to 1946 was minimal

in the presence of so great a dose of injected tubercle bacilli. The lungs had apparently filtered out the majority of injected bacteria, thus preventing, with the help of streptomycin therapy, hematogenous spread to the other organs of the body.

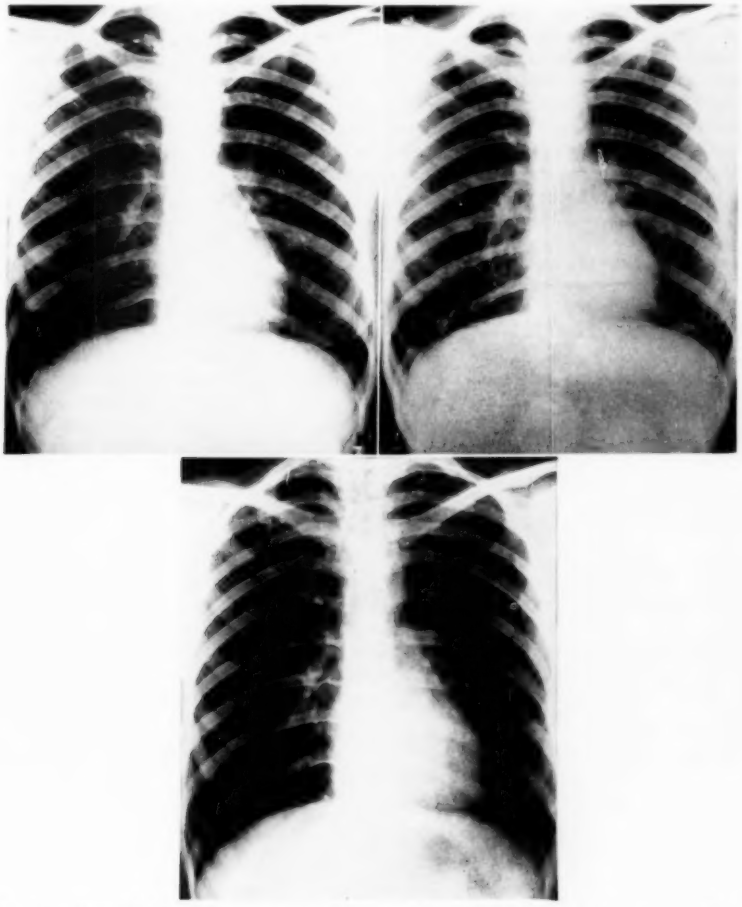

FIG. 6. (Upper left) Chest roentgenogram (April 8, 1948). Miliary areas are now beginning to fade, 72 days after infection and after 53 days of streptomycin therapy.

FIG. 7. (Upper right) Chest roentgenogram (May 7, 1948). Lesions in lungs still resolving.

FIG. 8. (Lower) Chest roentgenogram July 26, 1948 reveals no abnormalities.

There were available as indices of the success of streptomycin therapy the chest roentgenograms, determinations of the erythrocyte sedimentation rate and temperature readings, the local abscess at the site of injection, and the patient's subjective improvement. She remained on the original dose of streptomycin (3.0 Gm. daily) for nineteen days with

little or no definite improvement in the symptoms of general malaise, headaches, and shaking chills. Her temperature remained elevated with daily spikes to 103° to 104°F. During this time (February 19) a chest roentgenogram showed that the miliary lesions in the lungs were more sharply circumscribed and increased in number (figure 4). The lesion in her left antecubital fossa had not improved since the initiation of therapy. In the belief that larger doses of streptomycin might control the infection, the dose was increased to 5.0 Gm. a day and continued for four days without apparent improvement. The dose was then reduced to 2.0 Gm. of streptomycin per day because of the lack of improvement and severe vertigo.

At this time (February 23) the patient began to complain of a rather severe pain in the area of the venipuncture. Wet dressings were applied to the site of the injection and these seemed to give relief. On the following day, the puncture wound opened and considerable thick, yellowish pus was discharged. Following this, the patient's temperature dropped to 100°F. and remained there for seven days and then fell to 99°F.

From the twenty-third day of therapy, the patient's feeling of well-being improved dramatically. A roentgenogram of the chest taken on the thirty-eighth day of therapy (March 6, 1948) showed the lesions in the lungs to be static (figure 5) and the lesion on the left arm was definitely improved.

From the thirtieth day of therapy, the patient's temperature remained normal and a chest roentgenogram on the sixty-fifth day of treatment showed definite improvement in the lung lesions (figure 6). At this time (April 8, 1948) the lesion on the left arm had completely healed, and the patient had no symptoms except for moderate dizziness from the streptomycin therapy. No auditory changes were observed in serial audiograms.

One of the most fortunate factors aiding the recovery of this patient was the fact that the tubercle bacilli initially cultured from the lesion in the left antecubital fossa (Dubos medium) showed sensitivity to a concentration of less than 1.0 γ of streptomycin per cc.

The patient received a total of 241.0 Gm. of streptomycin over a period of 105 days. She was discharged to her home on her one hundred and twenty-fifth hospital day with no recurrence of symptoms following cessation of therapy. Her last roentgenogram obtained three weeks before discharge (figure 7, May 7, 1948) showed the lesions in the lungs to be less intense and more sharply circumscribed than on previous examinations. The erythrocyte sedimentation rate at the time of discharge was 21 mm. in one hour.

This patient has been carefully followed and a report from her physician in July 1948 stated that she was exercising moderately, felt well, and had gained weight. A chest film, July 26, 1948, revealed no abnormalities whatsoever (figure 8).

A letter received in October from this very fortunate young lady stated she had been working since September in a blood bank in the hospital of her home town. She also stated that her health was fine and confirmed this statement by the news of her marriage in early September 1948.

DISCUSSION

A review of the literature has revealed only one other case similar to the one presented here. The case of Lemierre and Ameuiée was that of a twenty-nine-year-old male who injected himself with a large dose of tubercle bacilli intravenously and developed miliary tuberculosis, shown in serial roentgenograms of his lungs, between the ninth and thirty-sixth day after injection. In this case streptomycin was not available, and the patient died at the end of three months. There were several significant differences between these two cases:

1. The French patient, without the aid of streptomycin, became progressively worse and roentgenographic examinations revealed increased size and distribution of the pulmonary lesions. Twelve days before death, the pulmonary lesions became confluent and caused marked respiratory embarrassment. Moreover, splenic enlargement persisted and the patient developed tuberculous meningitis eight days before death.

2. In contrast, in the present case the lung had apparently filtered out the tubercle bacilli, preventing further hematogenous spread.

3. The French patient did not develop anemia in spite of severe wasting and malnutrition.

4. Our patient showed normal leukocyte and differential counts throughout her illness. The French patient demonstrated a leukopenia, 2,600, and a mononucleosis at the beginning of his illness. This gradually reverted to normal and then to a leukocytosis of 12,500 with 90 per cent polymorphonuclear leukocytes in the terminal stage of his disease.

5. Our patient developed an initial fever immediatly after the injection lasting forty-eight hours, and then her temperature remained normal for nine days before rising to 104°F. The French patient developed a fever within forty-eight hours which persisted until death three months later.

The similarities between the two cases were:

1. The mode of injection was intravenous in both cases.

2. The latent period from the time of injection to the appearance of pulmonary lesions was between sixteen and twenty-one days in our case, and between nine and thirty-six days in the French patient.

3. Both patients had a positive tuberculin skin test prior to the injection of tubercle bacilli.

4. In neither case was it possible to obtain tubercle bacilli on cultures of the blood on Petragnani and Dubos media in our case and Loewenstein's medium in the French case.

It is believed that everyone will agree that this case presents one of the most interesting experiments in the pathogenesis and treatment of hematogenous tuberculosis in the human ever to be recorded. A careful attempt was made to note all of the pertinent facts which could be observed and determined through the study of this patient.

At the outset of the infection, it was suggested that the original site of the puncture should be totally excised but it was decided not to do this. It now appears that the procedure might have been beneficial, as the subsequent course of the patient showed very clearly that the streptomycin therapy had no effect on the infection until the original feeding focus sloughed out. The fall in temperatue and the loss of symptoms coincided very definitely with the evacuation of the original abscess.

The possibility exists that certain cases of miliary tuberculosis might be saved by the combination of streptomycin therapy and the eradication through surgery of the area in the body from which the tubercle bacilli are disseminating.

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ABDOMINAL PNEUMOCELE FOLLOWING ARTIFICIAL PNEUMOPERITONEUM[1]

H. C. WORTMAN[2] AND H. E. BASS

(Received for publication March 4, 1949)

Artificial pneumoperitoneum has become an accepted treatment for pulmonary tuberculosis. Recent months have seen an increasing number of reports regarding the results of this form of therapy (1-4). A comprehensive monograph has also been devoted to the subject (5). Aside from the latter work, little if any mention has been made of the roentgen appearance of air-containing circular shadows or pneumoceles in the abdominal cavity following artificial pneumoperitoneum. The following case reports are presented to illustrate the roentgenographic features of this condition.

CASE REPORTS

Case 1. The patient was a 24-year-old white male who developed cough and dyspnea in December 1945. He was admitted to a naval hospital in March 1946. The sputum was positive for tubercle bacilli and roentgenographic examination showed evidence of left upper and lower lobe cavitation with a right upper lobe infiltrate. A right pneumothorax was attempted in June 1946 but was unsuccessful. A left phrenic crush was performed in December 1946. In May 1947, a left pneumothorax was unsuccessful in closing the left upper lobe cavity. He was admitted to Halloran Veterans Administration Hospital in June 1947 and the left pneumothorax was continued until March 1948, when it was abandoned. On March 7, 1948 a pneumoperitoneum was initiated with good elevation of the diaphragm. In July 1948, the patient's sputum became negative for tubercle bacilli and has continued negative to the present time. Since September 1948, the cavities previously seen are no longer visible on chest roentgenograms.

Shortly after the initiation of the pneumoperitoneum, a pneumocele was demonstrated on the right side, just above the upper surface of the liver (figure 1). Subsequently, the intra-abdominal pressures were increased for therapeutic reasons by means of increased refills given at more frequent intervals. A film taken at this time (figure 2) showed increased ballooning of the pneumocele, which now extends almost to the lateral wall of the abdominal cavity. A film taken just before a refill during a period of decreased abdominal pressure showed some collapse of the air-containing shadow which exhibited an indented, serrated border (figure 3).

Case 2. The patient was a 40-year-old white male who on routine separation film in October 1945 was found to have an exudative infiltrate involving the entire right upper lobe with cavitation and spread of disease to the left second and third interspaces with multiple small cavities. The sputum was positive for tubercle bacilli.

A right pneumothorax was instituted at a naval hospital in November 1945 but numerous adhesions prevented adequate collapse. A left pneumothorax was initiated in January 1946, but was abandoned as ineffective. In May 1946, following an unsuccessful attempt at pneumonolysis, a right pleural effusion developed and the pneumothorax on the right side was also discontinued. The aspirated fluid was positive for acid-fast bacilli and the patient began running a toxic course. In August 1946, he was started on a course of streptomycin

[1] Published with the permission of the Chief Medical Director, Department of Medicine and Surgery, Veterans Administration, who assumes no responsibility for the opinions expressed or conclusions drawn by the authors.

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for 120 days with clinical improvement. In February 1947, there was a spread of disease in the left lung and streptomycin was again given for a 120-day period. Pneumoperitoneum was instituted with the hope that it would help control his disease so that thoracoplasty might be performed at a future date.

The patient was transferred to Halloran Veterans Administration Hospital in June 1947. The pneumoperitoneum was continued. He showed subjective improvement in spite of extensive bilateral disease with cavitation. In May 1948, the patient developed a spontaneous pneumothorax on the right side with a small amount of fluid. The pneumoperitoneum has been maintained.

A roentgenogram taken during the course of pneumoperitoneum therapy (figure 4) showed a pneumocele in close proximity to the upper surface of the liver.

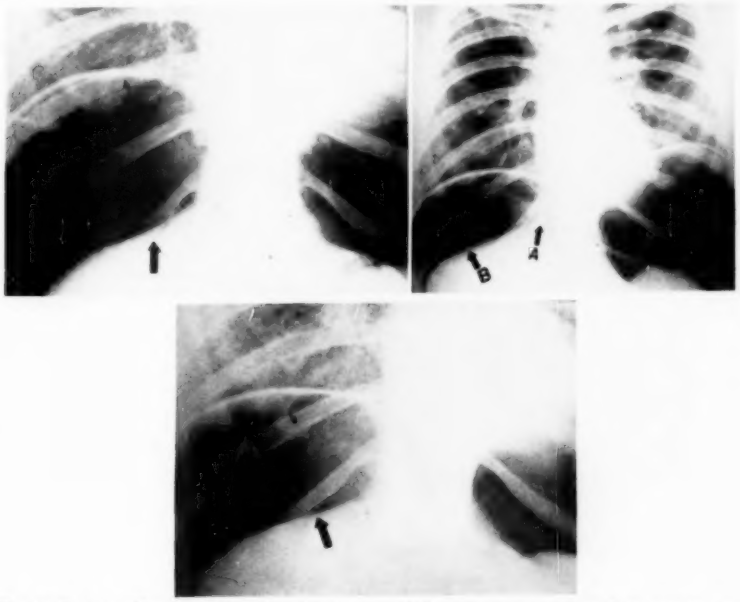

FIG. 1. Case 1. (Upper left) A circular air containing cyst or pneumocele is seen between diaphragm and liver on right side.

FIG. 2. Case 1. (Upper right) Ballooning of pneumocele with increased pressure. A. Shadow of falciform ligament. B. Pneumocele.

FIG. 3. Case 1. (Bottom) Deflated pneumocele following decreased intra-abdominal pressure, showing indented, serrated outline.

DISCUSSION

The appearance of these abdominal pneumoceles may be readily understood if the various peritoneal surfaces and reflections of the upper abdominal cavity are considered.

The visceral peritoneum covering the anterior surface of the stomach is continued between the stomach and liver, forming the anterior layer of the lesser omentum. It next invests the inferior, anterior, and upper surface of the liver. At the posterior portion of the

upper surface, it leaves the liver and goes to the diaphragm to form the anterior layer of the coronary ligament. Proceeding further, the peritoneum covers the anterior part of the dome of the diaphragm and on reaching the anterior abdominal wall is continued as the parietal peritoneum of the general abdominal cavity.

The visceral peritoneum covering the posterior surface of the stomach extends from the lesser curvature to the liver thus forming the posterior layer of the lesser omentum. It continues upward, investing the posterior surface of the liver, and is then reflected onto the diaphragm to form the posterior layer of the coronary ligament. Thus, this portion of the omental bursa behind the liver, known as the superior recess, is in direct communication with the general abdominal cavity (greater sac) through the epiploic foramen.

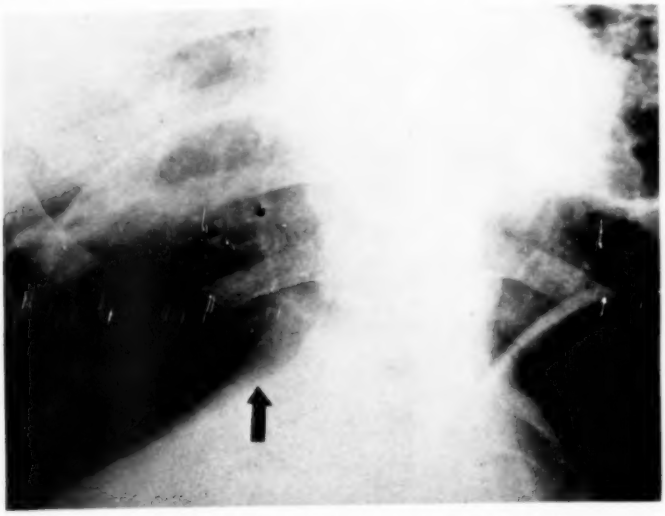

FIG. 4. Case 2. Pneumocele just above upper surface of liver.

The falciform ligament extends forward and downward along the anterior abdominal wall to the umbilicus as a peritoneal reflection from the anterior layer of the coronary ligament. This represents the anterior portion of the primitive ventral mesogastrium of the embryo.

From the above anatomical considerations of the peritoneal reflections of this subdiaphragmatic area, it becomes evident that with the elevation of the diaphragm from the liver there must be a resultant stretching and thinning of these peritoneal ligamentous attachments. The lesser sac posteriorly and the greater sac anteriorly are in direct communication below via the epiploic foramen but are separated above by the transversely situated coronary ligament. The falciform ligament connects the anterior portion of the coronary ligament to the anterior abdominal wall, thus restricting posterior displacement of the transverse coronary ligament. There is, however, no such restricting mechanism to prevent anterior ballooning or displacement.

The anatomical explanation offered appears to be borne out by fluoroscopic examination of the cases presented. The ballooning is anterior in the direction of least resistance, and to the right of the falciform ligament wherein lies the greater expanse of the right coronary ligament.

It is believed, therefore, that, dependent upon individual anatomical variation and upon differences in intra-abdominal pressure tensions upon the correspondent portions, the appearance of pneumoceles or peritoneal balloons may be expected in certain individuals receiving artificial pneumoperitoneum.

SUMMARY

1. The appearance of pneumoceles, or peritoneal ballooning, was observed in two cases receiving artificial pneumoperitoneum therapy for pulmonary tuberculosis.
2. An anatomical explanation for the appearance of these pneumoceles is offered.

SUMARIO

Neumoceles Abdominales Consecutivos al Neumoperitoneo Terapéutico

1. En dos casos en que se aplicó el neumoperitoneo terapéutico por tuberculosis pulmonar, se observó la aparición de neumocele, o inflación peritoneal.
2. Ofrécese una explicación anatómica de la aparición de esos neumoceles.

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PNEUMOPERITONEUM COMPLICATED BY INGUINAL HERNIA[1]

Report of a Case

WILLIAM J. McAULIFFE AND RICHMOND DOUGLASS

(Received for publication April 11, 1949)

Therapeutic pneumoperitoneum as a form of immobilization of the tuberculous lung has been used widely since 1935. The procedure is simple and the complications are few. Banyai (1) discusses air embolism, accidental pneumothorax, and mediastinal emphysema and mentions the appearance of pneumocele and coexistence of hernia among miscellaneous complications. Bennett (2) in 1938 reported discontinuing pneumoperitoneum in 3 cases because of the appearance of hernia. Monto and Bradford (3) in 1943 reported a case of pneumocele following pneumoperitoneum. The pneumocele was treated by the application of a pressure pad over the internal inguinal ring after the air had receded from the processus vaginalis. Apparently the pressure caused obliteration of the sac for the pneumocele did not reappear on subsequent refills. Daniels and Eisele (4) in 1938 mentioned 2 cases with inguinal hernia in whom scrotal pneumocele developed following pneumoperitoneum. These were treated with trusses.

A case of inguinal hernia treated surgically is reported because of the limited mention of hernia as a complication of pneumoperitoneum and because no report of surgical treatment has been found after intensive search.

A. R. (BMH 37025), a 25-year-old, single, white female was admitted by transfer from another hospital to the Hermann M. Biggs Memorial Hospital on October 28, 1948 for continuation of treatment for pulmonary tuberculosis which was moderately advanced and was active. The history revealed the onset of illness in January 1938 and the clinical course was characterized by recurrent hemoptyses and repeated hospitalizations, during which she was on a variety of therapeutic regimens. In May 1948, with cavity present on the left and a sputum positive for M. *tuberculosis*, pneumoperitoneum, supplemented by crushing of the left phrenic nerve, was instituted and maintained with weekly refills of 1,000 cc. Immediately after the induction of pneumoperitoneum the patient noticed a small lump in the right groin which had a peculiar "crackling" feel. Coughing, sneezing, or straining in any way caused the lump to become prominent but it always receded with relaxation. These findings were confirmed by her physician, but no treatment was instituted.

On admission to the Hermann M. Biggs Memorial Hospital, the physical examination revealed an asthenic, pale, thin, young adult, white female lying quietly in bed. The positive physical findings were limited to the chest and abdomen. There were post-tussic crepitant rales in the right apex and slight abdominal distention with absence of liver dullness. Routine examination revealed no abnormality in the right groin.

Fluoroscopy and roentgenograms of the chest revealed paradoxical motion of the left diaphragm which was at the level of the fourth anterior rib, and showed a normally functioning right diaphragm at the level of the fifth anterior rib. There was also noted scattered infiltration in both hilar regions.

Laboratory data: The erythrocyte and leukocyte counts were within the range of normal, and examination of the urine revealed no abnormal findings. There was no sputum for examination. Cultures of the gastric washings taken on admission were negative for tubercle bacilli.

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[1] From the Surgical Service, Hermann M. Biggs Memorial Hospital, Ithaca, New York.

On November 3, 1948, six days after admission, the patient complained of a slightly painful lump in the right groin. Examination revealed an irreducible right indirect inguinal hernia. She was placed in Trendelenburg position with hot water bottles to the abdomen and given 10 mg. of morphine. After a few hours another attempt at taxis was successful. The hernial sac filled with air, however, and a lump in the groin persisted. It was believed that pneumoperitoneum would aggravate the condition and that strangulation might occur. Because of the universally satisfactory response of congenital inguinal hernia to surgery (5), operation was decided upon.

Under spinal anesthesia a 10 cm. incision was made above the right inguinal ligament. The external spermatic and cremasteric layers were opened, exposing the sac of an indirect inguinal hernia lying anteromedial to the round ligament. The sac, which contained air but no bowel or omentum, was transected without opening and the proximal stump ligated with a suture-ligature of number 00 black silk after it had been tightly twisted. The distal portion of the sac was found to extend down to the insertion of the round ligament and included a tiny hydrocele. The hernial defect was then repaired according to the Ferguson technique. The wound healed per primam, the skin sutures being removed on the fifth postoperative day. Pneumoperitoneum refills were resumed on the fourteenth postoperative day.

This case illustrates the conversion of a congenitally patent processus vaginalis to a pneumocele following induction of pneumoperitoneum, with eventual herniation of abdominal viscera. Surgical repair was preferred to the method of pressure over the internal ring. Pneumoperitoneum and pulmonary tuberculosis were not regarded as contraindications to operative repair, particularly with the use of spinal anesthesia. Heriorrhaphy was, therefore, done and pneumoperitoneum continued.

SUMMARY

1. An inguinal pneumocele appeared in a 25-year-old woman immediately after induction of pneumoperitoneum.
2. A right inguinal hernia which was reduced with difficulty occurred six months later.
3. Repair of the hernia was carried out under spinal anesthesia without interrupting the therapeutic pneumoperitoneum and without adverse effect on the patient's clinical course.
4. Pneumocele occurring in the inguinal region during pneumoperitoneum indicates a congenitally patent processus vaginalis and, since this is amenable to surgery, operative repair is indicated.

SUMARIO

Neumoperitoneo Complicado con Hernia Inguinal. Observación

1. En una mujer de 25 años se presentó un neumocele inguinal inmediatamente después de ejecutarse un neumoperitoneo terapéutico.
2. Seis meses después apareció una hernia inguinal derecha que fué reducida con dificultad.
3. La hernioplastia fué lleavada a cabo con raquianestesia sin interrupir el neumoperitoneo terapéutico y sin efecto adverso sobre la evolución clínica del caso.
4. La aparición de un neumocele en la región inguinal durante el neumoperitoneo indica la existencia de un proceso vaginal congénitamente permeable, y como puede ceder a la cirugía, está indicada una operación plástica.

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EDITORIAL

The Cost of Tuberculosis Research

Elsewhere in this number of the American Review of Tuberculosis is an article by Virginia Cameron, Medical Research Secretary of the National Tuberculosis Association, in which an analysis is made of the cost of research on tuberculosis for a twelve-month period in 1947–1948. The report is objective and no attempt is made to determine whether the amount is inadequate or excessive, or if the results of the researches financed in that year justified their cost. The analysis does show, however, that the current annual expense for conducting research on tuberculosis in the United States exceeds six million dollars, that the majority of the sum currently spent is in the field of chemotherapy, and that the two chief contributors to the total cost are the Federal Government and industrial firms engaged in the production of pharmaceuticals.

It is not surprising that the total amount of money spent on tuberculosis research is large. In terms of lives lost, tuberculosis has been the most destructive disease in all history. Recovery from the disease, however, is as astonishing as its ravages, and the circumstances under which recovery occurs have stimulated an immense amount of investigation, ranging in the past from the most critical to the utterly absurd in efforts to develop a consistently successful means of control or cure. In their sum these efforts have been notably productive, if still falling far short of their goal.

Until relatively recently little of this research has been sponsored or stimulated by other than individual original interest. Personal interest, however, has always been a powerful source, and the governmental and organizational support characterizing the present period could accomplish little without the spontaneous spirit of inquiry of individual investigators.

A brief review of past achievements will show that every development in the control of tuberculosis has resulted from research. Understanding of the fundamental nature of the disease came from a long series of patient anatomical studies by Sylvius, Laennec, and scores of less well-known investigators. Their studies in turn paved the way for the discovery of physical diagnostic methods by Auenbrugger, Corvisart, and Laennec, and the immense amount of detailed clinical investigation which followed. The development of experimental medicine, to which Claude Bernard contributed so notably, and of bacteriological methods by Augostino Bassi and Jacob Henle and their early associates, opened the road for the specific investigations on tuberculosis by Villemin and Koch. In a purely physical investigation William Conrad Röntgen discovered X-rays, but within a few months surgeons applied the discovery to clinical medicine, and chest X-ray photography was a natural development.

It must not be forgotten, however, that each major discovery in medicine has resulted only through the summation of a vast number of major and minor discoveries in the same and quite different fields. The tubercle bacillus would not have been discovered without the microscope and the microscope could not have been invented and improved without exhaustive physical and mathematical in-

vestigation of refracting lenses. X-ray photography would be impossible without suitable light-sensitive materials, which did not become available purely by accident. Modern laboratory and clinical diagnosis of tuberculosis, its sanatorium, surgical and chemotherapeutic treatment, and the facts of epidemiology and public health, all have resulted from a synthesis of a huge amount of research. Chance entered into many important observations, but exact investigation has always been the next step after a lucky accidental find.

The productivity and ultimate value of medical research are seldom in direct proportion to its cost. Many of the greatest discoveries have been at little expense. Jenner's development of smallpox vaccination was of small cost to himself and none to any sponsoring agency. The outstanding investigation in the history of tuberculosis, the discovery of the tubercle bacillus, was made in the course of the normal duties of a section chief in the German Imperial Department of Health, Robert Koch. His personal industry and unquenchable curiosity, and the recently acquired background in bacteriological method which he had himself done much to develop, resulted in this major event in the history of tuberculosis without proportionate cost. Interestingly enough, had he not discovered the tubercle bacillus, little delay in its detection would have occurred, for Paul Baumgarten was but a few steps behind him and actually did report his own discovery a few days later. Confirmation of the studies of the two men came quickly from many sources, and again at little cost. Simple laboratory procedures for the detection of the tubercle bacillus in sputum and other pathological material were soon developed and readily available throughout the world.

In contrast, certain other and equally important fields have had to be cultivated on a much more expensive scale to yield comparable results. Perhaps no tool is more valuable in the diagnosis and care of tuberculosis than the X-ray. Millions of dollars have gone into the development and improvement of X-ray equipment since Röntgen's discovery of the ray a little more than fifty years ago. In view of the enormous value of X-ray photography in tuberculosis, the great cost has been well warranted. The far cheaper development of bacteriological diagnosis has been simply a happy circumstance.

The cost of all scientific research is rising and probably in greater degree than costs in general. The Curies' discovery of radium was at trifling expense compared with the cost of current investigations on nuclear fission. Extremely expensive equipment is essential for new advances in this field, and progress in other fields, including the development of new knowledge of disease, is analogous in its demands for better tools and methods. It is trite that research stimulates new research, but it is perhaps not so widely appreciated that the new research will almost always be more expensive than the old.

It has been suggested from time to time that some slackening in the general program of research on tuberculosis might now be justified, since progress up to date, as measured by the declining death rate, seems to indicate that the disease can be brought under complete control by procedures presently at hand. This is surely a short-sighted view of the future. No sufferer from the disease undergoing a long and tedious sanatorium course, even supported by daily injections of

streptomycin, is likely to be solaced by statistics if his own progress is doubtful, and no economist viewing the present annual hundred million dollar cost of sanatorium and hospital care of tuberculosis will be satisfied that no further investigation is needed. There may and should be argument as to the direction new research should take, and particularly as to the relative proportions of developmental, basic, and applied investigation, but adequate perspective will convince every thoughtful observer of the need for improvement in methods; and there is no escape from the fact that all improvements, in their very nature, result from some kind of research.

It could well be argued, however, that a large sum, greatly exceeding present expenditures, might be used still more profitably to speed up the present apparently productive program. Something of this character has been suggested by the National Planning Association (Planning Pamphlet No. 62, *Good Health is Good Business*, Section 1, *Tuberculosis: Why not get rid of it?*). The plan proposed calls for universal X-ray examination, expanded facilities for treatment, improved health education, and a large rehabilitation program. Attention has been called to some of the difficulties inherent in operation of the plan (Dempsey, Mary, *Summary of Review of National Planning Association's Report*, National Tuberculosis Association, September 28, 1948), but it is noteworthy that even this plan calls for an expenditure of $3,000,000 a year for research in a ten-year program requiring an outlay of $321,000,000 a year in its peak years.

Detailed suggestions are not made in that plan as to the distribution of the $3,000,000 designated. The proposal for this sum is based on an estimated expenditure of $1,200,000 for tuberculosis research in 1943, an amount greatly exceeded by the actual expenditures for tuberculosis research in twelve months of 1947–1948, as Miss Cameron's analysis indicates. Presumably the figure was intended to be elastic, as medical research is opportunistic, as is well illustrated by trends in tuberculosis research since the advent of streptomycin.

It is impossible to avoid being arbitrary in naming any sum as appropriate for a tuberculosis research program. There appears to be some justification from industrial experience in the figure of one per cent of the national income set by Mr. John R. Steelman, Chairman of the President's Scientific Research Board, in his *Report to the President* as a "modest annual investment" for a national program of scientific research. This figure has proved a useful one for planning, and it may be noted in this connection that it has been employed by the National Tuberculosis Association in its own estimate of expenditure for research on tuberculosis.* The NTA estimate is not purely arbitrary, however, for it was based in large part on the fact that the present expenditure of the Association is less than that sum, while promising projects go unsupported for lack of funds.

It would seem wise for planning purposes to set up figures of as much signifi-

*The following resolution was adopted by the Board of Directors of the Association at its meeting on May 2, 1949: "Resolved, that commencing with the 1950 Seal Sale contract the proportion of Seal Sale funds allocated to the NTA shall be increased to six per cent, [from five per cent] one-sixth of which shall be allotted to the research program of the NTA."

cance as possible on the basis of recent experience in the several individual federal, industrial, foundation, and academic programs. Suitable estimates for this purpose could hardly be made without an analysis of current expenditures for research, indicating costs, sources of financial support, and types of investigation financed. Miss Cameron has presented such an analysis, which should be of great value at a time when interest in the investigation of tuberculosis is increasingly active and organizations like the Public Health Service and the National Tuberculosis Association are expanding their programs in this field.

Certain reservations must be made in accepting the figures cited, as Miss Cameron herself has indicated. As an example, the cost of research in large industrial firms will vary with systems of accounting employed, and it is difficult or impossible to estimate the research expenditure involved in the salaries of workers who collect new facts from daily routine experience. The research element in the large mass X-ray surveys now in operation cannot be calculated without full knowledge of the use made of the figures obtained. This knowledge is not available and hence a research cost cannot be estimated. Such surveys are primarily for case-finding purposes, but their results when properly analyzed are of great value for epidemiological understanding and further planning, and it would be logical to designate a portion of the cost as for research if all facts were known.

It is significant that the donors of the largest sums for investigations, the official health agencies and the manufacturing firms, contributed a high percentage of the total allocated for a single purpose, streptomycin research. If streptomycin had not appeared so promising it is safe to say that much less money would have been expended for chemotherapeutic research, and much less accordingly for all tuberculosis research, since the proportion of the total cost for chemotherapy alone in 1947–1948 was so high.

It is equally significant that organizations long concerned with basic and developmental investigations, *i.e.*, scientific foundations, the National Tuberculosis Association, its affiliates, and the universities, have continued to devote the majority of their resources, presumably in spite of many pressures when applied chemotherapeutic research is so alluring, to fundamental research. At the present time increasing emphasis on the need for new fundamental research is widespread. Had streptomycin proved as successful as the most optimistic enthusiasts anticipated, had it proved, for example, as effective as penicillin in certain types of pneumonia, it is probable that interest in basic investigation on tuberculosis would have declined. Actually, however, streptomycin research has raised more problems than it has answered, and the new problems, such as the nature of the antibiotic mechanism and the reason for bacillary resistance to the drug, can be solved only by fundamental laboratory research.

Similarly the recent numerous empirical studies on BCG vaccination, while indicating the practical value of the procedure, have brought to the front, as never before, the necessity for further studies on the virulence of acid-fast bacteria and the whole problem of pathogenesis. There is indeed good reason to believe that unless more powerful substitutes for streptomycin are found and BCG vaccination proves more widely effective than present conservative investi-

gators believe it to be, the investigative trend in both fields will be toward basic rather than applied research.

For these reasons it may well be that the current distribution of research effort, as revealed in the report by Miss Cameron, will not be representative of future periods. Her analysis provides, however, the perspective needed for evaluation of the present program in terms of its cost, and a good basis at the same time for future planning.

ESMOND R. LONG

LETTERS TO THE EDITORS

WHAT'S WRONG WITH "MASS X-RAY" SURVEYS?

To the Editors of the American Review of Tuberculosis:

Recent statements by Doctor James F. Brailsford, the eminent British radiologist, have raised some doubts in the minds of many as to the real value of community-wide surveys. At first glance it is easy to ridicule Doctor Brailsford's thesis and we may even fall into that common habit of Americans of believing that just because we do things in a certain manner in this country it is of course the only way to do it! A few of us in Tuberculosis Control, however, are not so sure that everything is peaches down in Georgia. We are even convinced that Doctor Brailsford may be partially correct, and what's more, not being content to just talk about it, we'd like to do something about it.

First, we're going to tell a little story (Albrecht, F. K.: Editorial in Current Medical Digest (April) 1949) and we'll let you be the judge:

John Doe reads in his newspaper, "Get your free X-ray at the George Washington School Building tomorrow between 8 and 10 a.m." Unfortunately the use of the term "free x-ray" is false, since it is being furnished by the State Board of Health and only because John Doe's taxes have helped to purchase the equipment.

John Doe enters the lineup of folks awaiting their X-ray at the school building and when he reaches the registry desk, who should be typing the registry cards but his next door neighbor, Mrs. Jones. She greets John and asks: "Is there any tuberculosis in your family?" This information is, of course, requested for good reason on the registry card. Terror strikes John's heart. Both his parents died in a sanatorium of tuberculosis, but if he says "Yes," little Mary, Mrs Jones's daughter, will not be allowed to play with little Willie any more. And so he gulps "No" and stumbles away in confusion. What if the film does show tuberculosis? Will the neighbor's wife find out? Maybe she will see the cards when they are ready to be mailed out to those X-rayed! The whole neighborhood will be talking and John is in an extreme state of confusion. The film reader is being paid so much per film, instead of a flat fee per hour and, even though he is a bit fatigued, he reads on and on and on until he comes to the 70 mm. film of John's chest. Either inadvertently, or because he doesn't know of the distortion inherent in small film, he calls it a "Cardiac." It really isn't enlarged at all. What happens now? John's survey card is marked "Cardiac." About six weeks later, the local Tuberculosis Society announces in the paper that all the negative cards for the recent survey have been mailed. John Doe becomes worried and sick with fear. Does he have tuberculosis? He must have, since he has not received a negative card! Has he infected little Willie and his loving wife? Does the next door neighbor know? It seems she has acted a bit distant lately.

John Doe does one of two things: Disconsolate and frustrated, he goes to a roentgenologist and pays $15, which he can ill afford, for a large film. After a few days he is told: "There is nothing wrong with you." Failing this procedure, our John sweats it out for a few weeks and finally receives the little card telling him to see his doctor, who also advises a large film, which this time however is paid for by the local Tuberculosis Society. Two more weeks transpire before the film is read and finally the news arrives: "Film of poor diagnostic quality—will require a retake." The doctor in the meantime has assured him that there was no tuberculosis in the film—"Just a heart condition!" What are the chances of John's becoming a cardiophobe? How would you feel? Or, suppose the film reader in all sincerity noted "Scoliosis, severe," or "Dextrocardia," or "Pulmonary fibrosis, cause undetermined?" What can be done about it?

What is our solution? Education, or should we say re-education. We must educate the general public who seem to know little if anything about tuberculosis except a lot of misconceptions they have picked up in school under the subject of Health Education. They have the feeling that by some remarkable gift or innate inherited power they alone will never contract the disease. They believe that you conquer disease by dropping a dime or a quarter in a tin can on a street corner, and, of course, by buying Christmas Seals. Why should they worry? Tuberculosis is something only poor people get and they hear it is almost wiped out.

Is it any wonder the general public may develop a phobia and fear toward being X-rayed? They are told absolutely nothing. All agree that they should not be sent the findings of the small film since the medical terms used would only terrify them. They should be told, however, that there are many reasons *other than disease* that may cause one to be called back for a large film. If the general public knew these things, there would not be the fear and terror occasioned when that fateful card arrives saying "See your doctor."

The introduction of mass chest radiography to the civilian population is no easy undertaking. It must be done without causing fear and anxiety in those found to have suspicious shadows in their chest films. It must also be done without inducing a false sense of security in those who are shown to have a normal chest film.

In a recent book *Photoradiography in Search of Tuberculosis* (Zacks, D., Williams & Wilkins, Baltimore 1949), Dr. David Zacks of the Massachusetts Department of Public Health presents his experiences covering twenty years in tuberculosis control. He raises the question as to the real worth of the so-called "fast tempo" surveys, wherein after a lot of publicity and ballyhoo a whirlwind campaign is carried on for a short time, after which it moves on like a traveling road show to another community, leaving in its wake and in the local health officer's lap a multitude of problems, headaches, and heartaches.

I quote from Dr. Zacks' text:

> The high pressure campaign technique requires multiple X-ray units, adequate technical and professional personnel and sufficient financial resources with ability for rapid community organization and high pressure publicity in order to arouse not only interest in the community, but also a willingness to participate personally in the X-ray program. The campaign approach is rapid, spectacular, and high-geared but its contribution to tuberculosis control may be equally fleeting. The author prefers the relatively slow, sustained, systematic attack upon the problem. . . . . .The plan proposed is based upon extensive community organization and adequate chest diagnostic facilities, in addition to the survey procedure. . . . . .In order to bring about individual acceptance of the (chest) examination, education regarding pulmonary tuberculosis is necessary. . . . . .The educational program must be continuous and purposeful in order to influence people.
>
> There is no question here of socialized medicine. Mass chest X-ray examination is an ethical attempt to get at the root of tuberculosis control. To attain this aim it must include the total population rather than groups chosen for accessibility or a willingness to participate. . . . . .The ultimate aim. . . . . .is the establishment of chest X-ray service which will be available on a permanent basis to all persons, either through private physicians, health departments or cooperating community health agencies. The attainment of these objectives will depend in large measure upon education, not only education of the people themselves but also education of official and voluntary health agency leaders.

No community-wide chest roentgenographic survey can be considered satisfactory unless it permits a correct diagnosis. All agree that the small films are for screening purposes only and that it is essential to secure a 14 by 17 film *and a clinical history* for ten-

tative and differential diagnosis. Yet it is extremely rare indeed for physicians to supply any clinical history or information with the large follow-up films they send in for interpretation. Thus the program is still a screening program. There is no excuse for failure to supply a very short history with 14 by 17 films. Any nurse or office technician should be able to elicit a short, concise, pertinent history from a patient. Since a large majority of 14 by 17 follow-up films sent in for interpretation are not of diagnostic quality one concludes that either John Q. Patient or the Tuberculosis Associations are paying thousands of dollars yearly for worthless films.

There is need to re-educate some of the medical profession. A good physician recognizes the limitations of his stethoscope and will not try to diagnose tuberculosis with it. He appreciates that one can appear hale and hearty and have clinical tuberculosis. If he is told that a suspicious shadow was found on the 70 mm. film and is advised to have the patient get a large film, he will not scoff at such advice or tell the patient there is nothing wrong with him. He will know his own limitations in reading large film and not be ashamed to seek advice and counsel from his colleagues if he has had no special training in such film reading. He will never make a diagnosis based only on shadows. If he does not wish to do the necessary follow-up measures, it is his privilege to solicit the aid of a private consultant or to turn it over to public health authorities. He should not expect a diagnosis from a roentgenologist or film reader based on some shadows on celluloid without furnishing a short provisional diagnosis or clinical history. He should try to furnish films of diagnostic quality if he expects a diagnosis. He will report his cases to the proper health authorities. Before criticizing community-wide surveys and declaring they are a step toward State medicine, he will ask himself: Am I really concerned with the health of all people, including the indigent, in my city or county? He will remember that the first 14 by 17 film is still a screening film and that it is needed by the official agency conducting the survey to check its small film findings and complete the necessary records. It does not mean that he or several other physicians in his community are not capable of reading film. He must appreciate that "overreading" of small film, while it can cause great concern to those notified to see their physician, is better than underreading, if we are to pick up early treatable tuberculosis. He will be careful not to unduly alarm his patients as a result of some congenital abnormality reported on the small film. He will recognize his responsibility, examining his patients who are contacts of known open cases. He is entitled to his opinion and criticism of mass roentgenographic surveys, but before he lends his voice to such proposals as the restriction of surveys in his community to school children only, he should either examine his conscience or buy some new medical books!

Proper steps should be taken to re-educate our small film readers. They should approach this task with due respect and be mindful of the havoc they can create by insufficient training or bad judgment. They should be very cautious about reporting enlarged hearts or telling a person to see his doctor because of some condition he has lived with for sixty years such as scoliosis or fibrosis. What can either the doctor or patient do about it? It is this kind of stupidity that is bringing down opprobrium on these community-wide programs. For this reason alone, there should be an A and B reader employed to read small film. It may be costly but it would reap large dividends in less worry and needless anxiety which is caused by overreading.

Maybe we directors can also stand a bit of re-education. Before criticizing the voluntary workers, the general practitioners, and others connected with these programs, we should ask ourselves whether we have done all in our power to help these people. We will hold seminars for the voluntary workers, dispel their confusion, and correct their mis-

conceptions. If they know what to do and why they are doing it, they will do better work. We will seek every opportunity to address County Medical Societies both before and after the units enter their locality, so as to clear up the many problems that may arise following such surveys.

The Tuberculosis Control Division of the state of Kansas has inaugurated a plan wherein the actual 70 mm. film is sent to the family physician on all cases with significant findings. The physician thus has the small film in his possession on which the suspicious area is indicated with a China pencil. He can keep it with the patient's record and it may prove of valuable use in later years as a base-line study. This is a step forward in educating our physicians, many of whom are skeptical about the value of small films.

Is this a big order? We think so, but we are sure there will be many who are glad to take up the challenge.

Division of Tuberculosis Control
Kansas State Board of Health
Topeka, Kansas.
June 27, 1949.

F. Kenneth Albrecht,
Director

LETTERS TO THE EDITORS

ROENTGENOGRAMS OF DIFFUSE PULMONARY LESIONS

To the Editors of the American Review of Tuberculosis:

I have been interested for some time in the diffuse pulmonary lesions which may give roentgenographic shadows resembling those of miliary tuberculosis. We had a small exhibit dealing with this subject at the last meeting of the National Tuberculosis Association in Detroit. Enough doctors have shown an interest in the problem to tempt me to go on and try to collect still further examples of this often very confusing situation.

At the present time I have listed the following conditions as capable of giving the diffuse type of lesion that I have described. I am sure that this list is not yet complete.

I. INFECTIONS
- a. Tuberculosis*
- b. Bacterial
  1. Streptococcus*
  2. Staphylococcus septicemia
  3. Brucellosis
  4. Tularemia
- c. Mycotic
  1. Moniliasis*
  2. Aspergillosis
  3. Coccidiodomycosis
  4. Actinomycosis
  5. Blastomycosis
  6. Histoplasmosis
  7. Torulosis
- d. Rickettsial
  1. Q fever
- e. Virus
  1. "Atypical pneumonia"
  2. Psittacosis
  3. Varicella
- f. Parasitic
  1. Schistosomiasis

II. INHALATIONS
- a. Industrial
  1. Silicosis*
  2. Asbestosis*
  3. Beryllium*
  4. Siderosis*
  5. Bagassosis
  6. Byssinosis
  7. Vanadium
  8. Silver
  9. Talc
  10. Aluminum
  11. Barium
- b. Other
  1. Vomitus*
  2. Lipiodol*
  3. Kerosene
- c. Thermal

III. NEOPLASMS
- a. Primary
  1. Bronchogenic carcinoma*
  2. Alveolar carcinoma*
  3. Pulmonary adenomatosis
- b. Metastatic
  1. Stomach*
  2. Liver*
  3. Prostate*
  4. Melanotic sarcoma*
  5. Hypernephroma
  6. Tongue
  7. Thyroid
  8. Breast
  9. Pancreas
  10. Ovary
  11. Uterus
  12. Chorioma
- c. Generalized
  1. Lymphoma
  2. Reticulum-cell sarcoma*
  3. Multiple myeloma

IV. BLOOD DISEASES
- a. Myelogenous leukemia*
- b. Polycythemia vera
- c. Sickle-cell anemia

V. GENERALIZED DISEASES
- a. Sarcoidosis*
- b. Erythema nodosum*
- c. Rheumatic fever
- d. Lupus erythematosus disseminatus
- e. Periarteritis nodosa*
- f. Loeffler's syndrome*
- g. Tropical eosinophilia*
- h. Cystic disease of the pancreas*
- i. Xanthomatosis
- j. Amyloidosis
- k. Scleroderma

VI. FIBROSIS—GRANULOMATOSIS—BRONCHIOLECTASIS
- a. Fibrosis*
- b. Granulomatosis*
- c. Bronchiolectasis*
- d. "Acute interstitial fibrosis"
- e. Bronchiolitis fibrosa obliterans

VII. CIRCULATORY DISTURBANCES
- a. Pulmonary edema*
- b. Hemosiderosis*
- c. Emboli and infarcts
  1. "Phlebitis"*
  2 Lipiodol*
  3. Fat

The starred diagnoses in the above list are the conditions of which I already have a good example, and most of these roentgenographic reproductions were shown in the 1949 Exhibit.

I am anxious to get good examples of the conditions in the above list which are not starred or of any other conditions of which other doctors may have examples. I thought you might believe it worth while to publish this letter in the American Review of Tuber-

culosis to inform the men particularly interested in respiratory diseases throughout the country that we are trying to increase our collection of examples of diffuse pulmonary lesions and, if they have a roentgenogram of the type of case for which we are looking, I would appreciate it very much if they would mail the film to me with a very brief summary of the case and a statement of the test which proved the diagnosis given. We will then have a transparency made from the film and return the film itself to the sender. We will include the transparency in next year's exhibit and of course give credit to the man sending the film to us.

1101 Beacon Street
Brookline, Mass.
June 23, 1949

Donald S. King

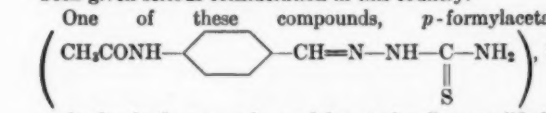
LETTERS TO THE EDITORS

ON THE ACTION OF THIOSEMICARBAZONES IN EXPERIMENTAL TUBERCULOSIS IN THE MOUSE

To the Editors of the American Review of Tuberculosis:

The antituberculous action of a number of thiosemicarbazones was first noted by Domagk, Benisch, Mietzsch, and Schmidt (Naturw., 1946, *10*, 315) in 1946, and preliminary clinical trials in man were described by Moncorps and Kalkhoff (Med. Klin., 1947, *42*, 812) in the following year. Recently several reviews in the German literature have included descriptions of the activity and pharmacology of some of these compounds (Heilmeyer, von L.: Deutsche med. Wchnschr., 1949, *74*, 161; Vinderbank, H.: Die Pharmazie, 1949, *4*, 198). Apparently the antituberculous activity of these compounds has not yet been given serious consideration in this country.

One of these compounds, *p*-formylacetanilide, 3-thiosemicarbazone



, has been studied *in vitro*, as well as *in vivo*, in the mouse in our laboratories. In a modified Kirchner's medium, containing Triton A-20 (a dispersing agent), the minimal inhibiting concentration for BCG was 0.0008 mg. per ml. In the mouse the maximal acceptable dose in the diet was found to be 0.032 per cent giving a daily dose of approximately 65 mg. per Kg. per day.

When administered at this maximal acceptable dose in the diet for 21 days to mice infected intravenously with the Ravenel strain of *M. tuberculosis* in a highly standardized test ((a) McKee, C. M., Rake, G., Donovick, R., and Jambor, W. P.: Am. Rev. Tuberc., 1949, *60*, 90; (b) Donovick, R., McKee, C. M., Jambor, W. P., and Rake, G.: Am. Rev. Tuberc., 1949, *60*, 109; (c) Rake, G., Jambor, W. P., McKee, C. M., Pansy, F., Wiselogle, F. Y., and Donovick, R.: Am. Rev. Tuberc., 1949, *60*, 121), deaths did not begin to appear until almost 40 days after infection, whereas all controls were dead before the thirtieth day. The minimal dose causing significant increase in T_{50} (50 per cent death time) was found to be approximately 0.004 per cent in the diet (equivalent to approximately 8 mg. per Kg per day) when treatment was started two days before infection.

Thus far, delayed treatment has been tried in only one experiment in which a level of 0.016 per cent in the diet (equivalent to approximately 32 mg. per Kg per day) was used. It was found that the compound was highly active at this level even when treatment was not started until 7 days after infection, and possibly active even when administration was delayed until 14 days post infection, in a test in which the T_{50} of the controls was 17.7 days, and some deaths had already occurred on the thirteenth and fourteenth days.

It is not possible at the time of this preliminary report to give a quantitative comparison between the action of this compound and other antituberculous compounds such as *p*-aminosalicylic acid. However, an indication may be obtained by noting that at 0.75 per cent in the diet, *p*-aminosalicylic acid gave T_{50} values of 24.0 and 30.0 days, respectively, in two tests in which the thiosemicarbazone was tested. In these tests the latter compound at 0.016 per cent in the diet gave T_{50} values of 35 and 45 days, respectively.

Extensive studies on the toxicology and pharmacology of this and related compounds are now under way in these laboratories.

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ABSTRACTS

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CLINICAL STUDIES, TUBERCULOSIS

Tuberculosis in Children.—Because of the diverse opinions regarding the proper management of tuberculosis in children, the courses of 234 patients hospitalized between 1942 and 1947 were reviewed. The ages ranged from five months to thirteen years. The criteria for admission were: (*1*) a positive tuberculin test, and (*2*) roentgenographic evidence of an active pulmonary or tracheobronchial lymph node lesion. On admission 79.5 per cent were diagnosed as having primary tuberculosis, 9 per cent had pleurisy with effusion, 6 per cent had miliary tuberculosis, 3 per cent had the reinfection type of tuberculosis, 2 per cent were nontuberculous, and one patient had tuberculous meningitis without a demonstrable pulmonary lesion. Of those with a primary infection, 89.8 per cent were asymptomatic and 89.3 per cent were afebrile. Only 17 patients (9 per cent) were considered to be chronically ill and 8 of these had a serious nontuberculous infection. Acid-fast bacilli were demonstrated in 20.4 per cent of this primary group. Six patients in the primary group developed tuberculous complications after admission and 3 were readmitted for complications after discharge. The average hospital stay was 250 days. Treatment consisted of a general, high caloric diet, cod liver oil, feosol tablets and complete bed rest. Restraining jackets were used on young children considered to be too active. The children of school age were allowed one hour daily of classwork. None of the children with a primary infection received specific therapy in any form and no streptomycin was used. Children were considered ready for discharge when there had been complete absorption of the parenchymal lesion and contraction or calcification in the regional lymph nodes. The hospitalization of these patients seems to offer only one advantage, the opportunity to diagnose a tuberculous complication in its early stages. This responsibility can well be taken over by the chest clinic.—*Tuberculosis in children, S. L. Painter, Dis. of Chest, March, 1949, 15: 329.—(E. A. Rouff)*

Initial Pneumothorax.—A new technique was devised to minimize the trauma during the induction of pneumothorax. A 2 cc. or 5 cc. syringe is fitted with a sharp, short-bevel, small needle. The syringe is half filled with either saline or procaine solution. The needle is advanced just through the skin and the plunger drawn back to be sure the connections are air-tight. No bubbles must appear in the fluid. The patient is then instructed to hold his breath in deep inspiration while the needle is advanced. Constant suction is maintained with the syringe until a few bubbles appear in the fluid. The needle is then immediately withdrawn. The bubbles have come from the superficial alveoli, and leakage of air from these alveoli into the pleura will continue for a varying period to produce a pneumothorax space. Occasionally insufficient air escapes to produce a visible space. In this event the procedure should be repeated. If several attempts fail to establish a pneumothorax, the pleural space has been previously obliterated. Comparison of this new technique with the present manometric method reveals that the initial, traumatic collapse was approximately half as

great when the new procedure was used. Furthermore, there were fewer instances of excessive, dangerous collapse.—*Initial pneumothorax: A new safe induction technique, I. J. Selikoff, I. G. Tchertkoff & E. H. Robitzek, Quart. Bull., Sea View Hosp., July, 1948, 10: 93.*—(*K. T. Bird*)

Follow-up of Collapse Therapy.—The fate of 94 patients who responded poorly to collapse therapy and one year's bed rest was traced during a follow-up period of five to twenty years. The mortality figures indicate the poor prognosis of those patients whose illness follows its course in an uncontrolled manner. Fifty per cent were alive after three years, 25 per cent after six years, and 10 per cent after ten years. These figures are in contrast to those of Düggelis, who compiled statistics from the same sanatorium on 486 patients whose sputa were negative for tubercle bacilli prior to discharge. Of these, 75 per cent were still living sixteen years later as compared with 3 per cent in the first group of poorly controlled patients.—*Ergebnisse der Kollapstherapie bei schweren Lungentuberkulosen, H. Hasler, Schweiz. Ztschr. Tuberk., 1949, no. 1: 1.*—(*E. Dunner*)

Basal Tuberculosis.—Of 1,379 known cases of tuberculosis, 21 (1.52 per cent) were found to have had a characteristic basal onset of their disease. The short interval between onset and diagnosis, averaging 30.6 days, with extension of the lesion to a moderate or far advanced stage in all cases during this interval, and the roentgenographic characteristics indicate that reinfection tuberculosis with a basal onset should be classified as an acute and progressive disease. The average age of the 21 patients was 25.8 years; the female:male ratio was 2.5:1. Early, active treatment is indicated; pneumothorax is preferable. The prognosis is good since 88.8 per cent of this series recovered and were known to have been well on an average of 72.3 months after diagnosis.—*Basal onset of reinfection tuberculosis, H. H. Cherry, Am. J. Roentgenol., January, 1948, 59: 82.*—(*J. E. Farber*)

Prognosis of Minimal Tuberculosis.—The importance of being able to estimate the activity of tuberculous lesions on the roentgenogram is obvious. Recent studies by Birkelo *et al.*, show that it is possible to estimate activity from the first roentgenogram in a relatively high percentage of cases. The present study was solely concerned with this prognostic factor of the roentgenologist's diagnosis in 1,100 patients followed for one month to nineteen years. Statistical examination of the data showed that there is considerable roentgenological error in prognosis but the progression rates and death rates indicate that the roentgenologist's opinion is of great value in determining the type of treatment for such cases.—*The value of roentgenology in the prognosis of minimal tuberculosis, A. L. Cochrane, H. W. Campbell & S. C. Stein, Am. J. Roentgenol., February, 1949, 61: 153.*—(*J. E. Farber*)

Minimal Tuberculosis.—A series of cases has illustrated the problems associated with the roentgenologic interpretation of minimal, pulmonary, reinfection tuberculosis. The classification of the roentgen picture on a pathological basis is not entirely satisfactory and considerable differences exist in the interpretation of the roentgenograms. Further study and correlation between necropsy and roentgenologic findings is required to establish the descriptive terminology on a more solid footing. It is hazardous to decide the prognosis or clinical significance of a lesion on the basis of one film or a few films. Pulmonary lesions may be minimal in extent and yet represent the end result of the closure of a tuberculous cavity. Round foci, linear horizontal scars, and stellate scars are examples of such lesions which may be interpreted incorrectly as minimal lesions with good prognosis. A minimal lesion can therefore best be evaluated if the whole history of the case is known. A more uniform roentgenologic interpretation of minimal tuberculosis might be possible if the National Tuberculosis classification included a statement of the total period of observation and whether the evaluation is made on the

basis of a series of films, a few films, or a single film. It would also be helpful to state, where possible, the length of time between the onset of illness and the date of the film.—*Minimal tuberculosis: Problems in roentgenologic interpretation, I. D. Bobrowitz & A. Hurst, Radiology, April, 1949, 52: 519.*—(*W. J. Steininger*)

Interpretation of Roentgenograms.—From this study by experienced radiologists and from previous work, it is established that the interpretation of roentgenograms is subject to a certain degree of inherent error. If a set of similar films is read by two different observers, the likelihood is that in 16 per cent of the cases the two readers will disagree with each other as to whether or not a lesion is present. If the same person re-reads the same set of films, he is likely to disagree with himself in approximately 8 per cent of the cases. The degree of error or variation is significant but compares favorably with that found in other clinical methods and diagnostic aids. The usefulness of studies on this phenomenon may be measured by the degree to which they are aimed at understanding the reasons behind the variations and by the discovery of methods to reduce them. The results of this study indicate that among the important reasons for "missing" a positive film are the size, location, and density of a lesion, as well as the "attitude" of the observer. A technique which permits a reader to review each "preliminary" positive may reduce significantly the percentage of positive cases missed without necessitating over-reading. For mass survey work it would appear imperative (*1*) to select the panel of readers with great care, (*2*) to submit them to valid tests, and (*3*) whenever practicable to utilize dual reading, which is actually an economical case-finding procedure. Much work is needed on methods of describing lesions and on rational evaluation of existing classifications. It is believed that the accuracy of chest diagnostic work will be enhanced as a result of basic studies of the type outlined in this report.—*On the scientific evaluation of diagnostic procedures, L. H. Garland, Radiology, March, 1949, 52: 309.*—(*W. J. Steininger*)

Tuberculous Calcification.—Calcification begins early in the development of caseating tuberculous lesions. It may be present without casting the usual roentgenographic shadow if the lesion is not packed with calcium. Of great clinical importance is the fact that a lesion which appears calcified may still be soft, caseous, and potentially dangerous.—*Tuberculous calcification—A clinical and experimental study, R. Bloch, Am. J. Roentgenol., June, 1948, 59: 853.*—(*J. E. Farber*)

Clinical Studies, Nontuberculous Diseases

Beryllium Pneumonitis.—When beryllium accidentally is introduced beneath the skin, chronic ulcers form and persist until the beryllium is removed. Surgeons have found also that beryllium alloys are unsatisfactory for repairing bony defects and lead to the formation of chronic granulation tissue. Exposure to dust and fumes containing beryllium has resulted in pulmonary disease of two clinical types: (*1*) an acute pneumonitis, and (*2*) a protracted pulmonary fibrosis with emphysema. Tissues from 7 patients who died of acute pneumonitis and from 13 who died of chronic granulomatosis induced by beryllium were studied. The pulmonary lesions in these two clinical conditions are specific and there is evidence of a transition from the acute lesions to the chronic ones. In the acute pneumonitis there is a boggy, generalized consolidation of entire lobes, simulating the stage of gray hepatization in lobar pneumonia. Microscopically, there is diffuse intraalveolar exudate composed of large mononuclear phagocytes (septal cells) and edema fluid. Intraseptal lymphocytes and plasma cells are fairly numerous also. Centrolobular necrosis of the liver was seen in one case. In chronic pulmonary fibrosis or granulomatosis, the lungs are voluminous and emphysematous with many fine nodules scattered diffusely throughout them. The right ventricle of the heart is always enlarged. Microscopically there is diffuse interstitial and nodular fibrosis of the lungs with a peculiar granulom-

matous reaction. The granulomas which are typical of beryllium disease are formed, in part, within the alveolar spaces by the organization of exudate, in part, within the septal and peritruncal connective tissue. Each has a central region of fibrinoid material or granular debris and this is surrounded by a peripheral zone of fibrosis infiltrated by lymphocytes and plasma cells. The centers of the granulomas are occasionally occupied by giant cells of the Langhans' type. There are conchoidal bodies in most cases, sometimes within giant cells, sometimes lying free in debris or in fibrous tissue. The granulomas in the lungs are of the same nature as those accidentally produced in the skin and subcutaneous tissues.—*The pneumonitis and granulomatosis peculiar to beryllium workers, F. R. Dutra, Am. J. Path., November, 1948, 24: 1137.*—*(J. S. Woolley)*

Thoracic Complications of Amebiasis.—Hepatic abscess complicates infestations by *Endamoeba histolytica* in about 5 per cent of cases. Fifteen per cent of these develop intrathoracic complications. The ratio of male to female patients is 15:1 for unknown reasons. The age range for most is 20 to 50 years. The hepatic abscess is solitary in 65 to 88 per cent and is in the right lobe in 85 to 96 per cent since the infection usually reaches the thorax by direct extension through the diaphragm and pleura and then to the lung. If the pleural layers are adherent, the lung is invaded directly. Abscesses from the left lobe of the liver may invade the pericardium but rarely involve the left lung or pleura. Rarely, solitary pulmonary abscesses not adjacent to the diaphragm are seen; these are probably embolic in origin. In 50 per cent of cases, there is no previous history of dysentery. The most usual complaint is pain in the right lower chest and shoulder. This is followed by a cough which at first is nonproductive. Later, there is hemoptysis which is followed by expectoration of sputum which looks like chocolate or anchovy paste. There is a septic type of temperature and there are other toxic manifestations. The roentgenogram shows a characteristic hump-like localized elevation of the diaphragm, best seen in the lateral view. If there is direct extension into the lung, a shadow is seen in the base of the involved lobe with its apex tapering off toward the hilus; this may contain a cavity with a fluid level. The pleural cavity may contain fluid or air and fluid; this may be general or loculated. If there is an abscess of the left lobe of the liver, roentgenogram of the stomach with barium will show it to be displaced posteriorly and laterally. The prognosis is worst if there is empyema, better if there is lung involvement alone, and best if there is a bronchohepatic fistula without pleuropulmonary involvement. The use of emetine greatly lowers the mortality: it should be used for all cases of hepatic abscess with or without pleuropulmonary complications. Surgery thus may sometimes be averted. If dysentery is present, carbarsone or diodoquine should be added. If hepatic abscesses are bulging, they should be aspirated repeatedly. Indications for surgery are: (*1*) secondary infection, (*2*) empyema incurable by aspiration, (*3*) persistent communication between the biliary tract and bronchi and (*4*) fibrosis of pulmonary tissue. The liver should be drained via an extraserous route. In empyema, thoracotomy and decortication of the lung and diaphragm should be done; the liver need not be drained. In pulmonary involvement, the damaged pulmonary tissue should be resected locally or by lobectomy. In pericardial infection, drainage should be done. Postoperatively, emetine and carbarsone or diodoquine should be given.—*Thoracic complications of amebiasis, R. R. Shaw, Surg., Gynec. & Obst., June, 1949, 88: 753.*—*(A. G. Cohen)*

Friedlander's Pneumonia in Infants.—Pulmonary infection with Friedlander's bacillus (*Klebsiella pneumoniae*) is very rare in infants and few cases have been reported. The lesions apparently lack the roentgenographic signs of abscesses or thin-walled cavities seen in adults. The disease may be epidemic. It fails to respond to sulfonamides and penicillin. Seven cases of atypical pneumonia are reported in infants of three weeks

to thirteen months of age. All but one had an insidious onset; all had signs of purulent bronchitis although two had normal chest roentgenograms; and each had a pure culture of *K. pneumoniae* from the throat. All failed to respond to penicillin and/or sulfadiazine but responded to the use of streptomycin.—*Pneumonia in infancy caused by Friedlander's bacillus, B. F. Grotts, J. Pediat., February, 1949, 34: 174.*—(*W. H. Oatway, Jr.*)

Histoplasmosis in California.—The occurrence of a mild subclinical form of histoplasmosis probably is widespread. Eighty-five California children with suggestive clinical symptoms were surveyed by tuberculin and histoplasmin tests. Five patients with positive histoplasmin tests and negative tuberculin tests were found to have multiple pulmonary calcifications. Coccidioidin tests were not done. Four of the five children had lived or visited in Texas, Wyoming, Arizona, or Missouri.—*Histoplasmosis in California children, Helen B. Pryor, J. Pediat., January, 1949, 34: 12.*—(*W. H. Oatway, Jr.*)

Erythema Nodosum.—There are three theories to explain the etiology of erythema nodosum: (*1*) that it is a manifestation of tuberculosis; (*2*) that it is a syndrome, a skin manifestation of several disease processes; (*3*) that erythema nodosum is an infectious disease of definite etiology, but that similar manifestations may occur "symptomatically" in other disease processes. The author's detailed histopathologic studies lead him to conclude that erythema nodosum is an independent disease of definite etiology, the causative agent of which is unknown. It is likely that certain diseases predispose the body to attack by the causative agent of erythema nodosum as they do to attack by the pneumococcus and herpes simplex virus. Apparently tuberculosis is only one of several diseases that create conditions favorable for the agent of erythema nodosum. Other predisposing causes are lymphogranuloma venereum, sarcoidosis, "atypical" pneumonia, certain streptococcal infections, and treatment with certain sulfonamides.—*Die Aetiologie des Erythema nodosum, G. Miescher, Schweiz. med. Wchnschr., March 27, 1948, 78: 269.*—(*H. Marcus*)

Linear Atelectasis.—Linear atelectasis frequently occurs in association with intra-abdominal lesions. Pathologically the atelectatic area is discoid; roentgenographically it usually appears as one or more striations. Typically these striations extend outward from the cardiac border in a horizontal or oblique direction across the lower third of one or both lung fields. Most frequently the shadows lie just above the diaphragm which is elevated and limited in motion. Linear atelectasis is always secondary to some other lesion, either intra-abdominal or intrathoracic. A total of 7,064 roentgenograms were examined, representing patients hospitalized for complaints of all types. In 29 (0.4 per cent), linear atelectasis was demonstrated. Three of the 29 cases were excluded from the series because no adequate primary source could be demonstrated. Among the remaining 26 cases, there were 22 (80 per cent) of intra-abdominal lesions and 4 (20 per cent) of thoracic lesions. The atelectasis occurred in 12 cases on the side of the involved organ, in 3 cases on the opposite side. It usually was transient but at times persisted for weeks or months. The presence of linear atelectasis, with or without a high diaphragm, affords presumptive evidence of disease within the abdomen.—*The linear atelectatic sign in intra-abdominal lesions, J. L. Marks & A. Nathan, Radiology, March, 1949, 52: 363.*—(*W. J. Steininger*)

Appearance of Lungs in Mitral Stenosis.—Aggregations of so-called "heart failure cells" in the lung parenchyma have been known for many years but their recognition by means of roentgenography is new and little known. The appearance simulates miliary tuberculosis The lesions probably arise because the mitral obstruction causes increased pressure in the left auricle and ultimately in the alveolar capillaries. These become engorged and may bleed into the alveoli. Hemoglobin from the disintegrating red blood cells is converted

into soluble iron-free hematoidin and insoluble particles of iron-containing hemosiderin. The latter, acting as foreign bodies, are phagocytized and carried into the lymphoid tissue of the lungs, finally reaching the bronchial lymph nodes. This movement probably is slower than that in pneumoconiosis because the chronic pulmonary venous congestion obstructs the lymphatic drainage, leaving most of the hemosiderin-laden cells in the alveoli. They are radio-opaque and produce the stippling observed on the roentgenogram. Seen through a hand lens, some of the minute shadows on the roentgenogram are ring-like with the form of a rosette, the central hole being the terminal respiratory bronchiole.—*Miliary appearances in the lungs in mitral stenosis: Endogenous pulmonary haemosiderosis, T. E. Gumpert, Brit. M. J., September 27, 1947, no. 4525: 488.*—(*R. W. Clarke*)

Pulmonary Embolism.—Pulmonary embolism may occur without infarction owing to the double circulation of the lungs. The characteristic roentgenographic findings are increased radiolucency and ischemia of the involved pulmonary segment. Abrupt termination of the embolic pulmonary artery is frequently demonstrable. This contrasts strikingly with the usual area of increased density on the roentgenogram found in cases of embolism with infarction.—*Pulmonary embolism without infarction, R. Shapiro & L. Rigler, Am. J. Roentgenol., October, 1948, 60: 460.*—(*J. E. Farber*)

Unresolved Pneumonia.—The use of this term is to be discouraged; proper study of the patient usually will reveal the correct diagnosis. Bronchiectasis, atelectasis, and intrabronchial disease, often in association with pneumonia, are commonly responsible for so-called unresolved pneumonia. Thorough roentgenoscopy, bronchoscopy, and bronchography may determine the underlying pathology.—*Unresolved pneumonia, C. L. Hinkel, Am. J. Roentgenol., March, 1949, 61: 335.*—(*J. E. Farber*)

Lipoid Granulomatosis.—In 1946, a 35-year-old man manifested general weakness and progressive dyspnea. Chest roentgenograms in 1938 and 1940 had revealed mottling throughout both lung fields. A film in 1946 showed extensive interstitial fibrosis throughout both lungs with moderate cardiac enlargement and prominence of the pulmonary conus. Roentgenograms disclosed a large defect in the right parietal region and cystic areas of bone destruction in both the femora and the left pubic bone. A biopsy specimen of the right parietal bone had the histopathologic picture of lipoid granuloma of the type seen in Schüller-Christian disease. Following deep roentgen-ray treatment to the chest, there was some clearing of the pulmonary infiltration. The patient, however, began to manifest cardiac decompensation which has progressed in spite of the usual therapy.—*Lipoid granulomatosis (xanthomatosis) with marked pulmonary fibrosis and cor pulmonale as outstanding manifestation, S. J. Schneierson & L. Schneider, Ann. Int. Med., April, 1949, 30: 842.*—(*H. R. Nayer*)

Mycotic Pulmonary Arterial Aneurysms.—A 10-year-old boy, who had no congenital defects, syphilis, or bacterial endocarditis, developed multiple pulmonary aneurysms. His illness began with a low-grade thrombophlebitis of the lower extremities. This phlebitis slowly extended to the inferior vena cava and the collateral circulation developed. Small septic emboli invaded the lungs, causing thromboendarteritis of the pulmonary arteries whose walls became fibrotic, weakened, and dilated to form multiple, large, mycotic aneurysms. Roentgenograms showed several enlarging, dense patches in the perihilar area. Following a septic course with repeated hemoptyses, the patient died and autopsy findings substantiated the clinical impression.—*Thromboendarteritis with multiple mycotic aneurysms of branches of the pulmonary artery, C. L. Pirani, F. E. Ewart, Jr., & A. L. Wilson, Am. J. Dis Child., April, 1949, 77:* 460.—(*W. H. Ootway, Jr.*)

Carcinoma of Lung.—A total of 604 patients in sixteen years were diagnosed as having primary carcinoma of the lung. The diagnosis was proved by biopsy in 481 cases; in the remainder it was established by reasonable clinical criteria. Of the patients, 85.5 per cent were men. Operation was advised unless (*1*) there was absolute or strong presumptive evidence that the tumor could not be resected or (*2*) the condition of the patient was too poor. Of the cases seen, 48 per cent were explored and resection was done in 27 per cent. In recent years, 51 per cent were explored and 32 per cent resected. The cases were divided into 3 groups: (*1*) no demonstrable extrapulmonary extension, (*2*) lymph node metastases only (gross or microscopic) and (*3*) gross evidence of extension. The average survival period of cases known to have died was 4.4 months for the inoperable group and 11.3 months for the group resected with no apparent extension. Among the resected cases, 24.4 per cent of those operated upon five or more years ago and 60 per cent of those operated upon one year ago or less are still alive. Of the cases resected with no apparent extension, 90.9 per cent of those operated upon during the past year were still alive, as were 33.3 per cent operated upon one to five years ago and 40 per cent of those operated upon more than five years ago. If operative deaths are excluded, the percentages rise to 100, 40, and 50, respectively. The average survival time of those dying postoperatively was 11.1 months, the longest time 28 months. If there was lymph node extension only, two-sevenths were alive more than two years later and 20 per cent were alive after five years. The average survival time of those dying was 9.6 months, the longest time 23 months. In the cases with gross extension, palliative resection was performed for many; in 24 cases, all detectable tumor tissue was removed. Only one of the 43 patients was alive after one year. The average duration of life was 10 months and the longest survival period was 29 months. The procedure of choice was pneumonectomy, except in 8 aged persons with a localized tumor, for whom lobectomy was performed. Four survived more than two years but all are dead; 4 operated less than two years ago are all living. The pathological types were (*1*) undifferentiated, (*2*) carcinoma rising from glandular epithelium and (*3*) epidermoid. The following statistics pertain only to those patients who survived the operation. In the group with undifferentiated carcinoma, none was living after three years. The average duration of life was 9.3 months and the longest survival 29 months. In the adenocarcinoma group, one of 6 is alive after three years; the average duration of life was 10.2 months. In the carcinoma simplex group, none is alive after one year; the average duration of life was 7.3 months. In the epidermoid group the results were: grade I, 40 per cent alive after two years, 37.5 after three years, 40 per cent after ten years, with an average survival time of 15.1 months and a maximum of 27 months; grade II, 44.4 per cent alive after three years. 50 per cent after five years, with average survival time of 12.9 months and a maximum of 24 months; grade III, 50 per cent alive after five years, with an average survival time of 8.4 months and a maximum of 28 months. Altogether 10 patients are living after five years. No patient who lived for 30 months later died of the disease.—*Survival in primary carcinoma of the lung, R. H. Overholt & I. C. Schmidt, New England J. Med., March 31, 1949, 240: 491.*—(*A. G. Cohen*)

Cytologic Diagnosis of Lung Cancer.—From 671 cases of suspected lung cancer or undiagnosed chest disease, 2,228 sputum specimens or bronchial aspirates were submitted to cytologic examination. Of these 671 cases, 100 proved to be carcinoma of the lung. Sputum from 89 of the 100 proved cases was examined and cells "consistent with malignancy" or "suspicious" were found in 63 (71 per cent). Secretions obtained bronchoscopically from 45 proved cases were studied and positive findings were reported in 26 (58 per cent). It was found necessary to examine at least 3 slides from each of 5 daily sputum specimens before the cytologic examination could be considered adequate.

When these complete studies were made, the accuracy of cytologic diagnosis was increased to 90 per cent (63 of 69 proved cases). On the other hand, the number of specimens examined was inadequate in 20 of the 26 proved cases missed by sputum examination; in 12 cases a single specimen was submitted. When sputum and bronchial aspirates from the same cases were examined, the results were comparable. The relative ease with which sputum smears may be prepared makes this diagnostic procedure available where adequate diagnostic facilities, such as bronchoscopy, are lacking. However, the technique of cytologic examination has definite limitations and further evaluation under rigid investigative control is necessary before it can take its proper place in the diagnosis of bronchogenic carcinoma.—*Diagnosis of bronchogenic carcinoma by cytologic methods, S. M. Farber, M. A. Benioff & A. K. McGrath, Jr., Radiology, April, 1949, 52: 511.*—(*W. J. Steininger*)

Aspiration Biopsy of Lung Lesions.—During the years 1936 through 1947, the authors performed needle biopsies on 272 lesions of the lung, in 231 patients. Of these patients, 220 were suspected of having bronchogenic carcinoma not accessible to bronchoscopy. In 11 patients, the biopsy was done for other suspected intrathoracic lesions but lung tissue was traversed. Of the 220 patients, 163 were proved to have carcinoma of the lung by a definite pathologic report on material obtained by needle biopsy, by subsequent bronchoscopic biopsy, or by exploratory thoracotomy which was used as the final resort; 135 were proved to have pulmonary carcinoma by needle biopsy. The positive diagnosis rate was, therefore, approximately 61 per cent. There was one false positive result. The method lent itself especially well to soft carcinomas located peripherally in the lung. There was little success in diagnosing firm, solid, benign lesions or lymphoblastomas. The procedure is simple but not without hazard and should be used only when a definite diagnosis of carcinoma cannot be made by bronchoscopy or sputum analysis. Complications developed following 20 (7.3 per cent) of the needle biopsies. Three patients died shortly after the procedure: one from tension pneumothorax, one from shock and convulsions, and the third from coronary thrombosis. There were only two serious pneumothoraces, both in patients with marked emphysema which makes the procedure hazardous. One patient developed a central facial palsy within seven days and died later of metastatic tumor. No case of empyema developed and there was no evidence of the spread of tumor along the needle track. The method is relatively useless unless a biplane or multiplane fluoroscope and a competent fluoroscopist are available. The pathologist must be willing to make a diagnosis from a very small specimen.—*Value and limitations of aspiration biopsy for lung lesions, G. P. Rosemond, W. E. Burnett & J. H. Hall, Radiology, April, 1949, 52: 506.*—(*W. J. Steininger*)

Dysgerminoma.—Invasion of pulmonary tissue by dysgerminoma has been demonstrated only rarely in the living patient. A 48-year-old white woman survived seven and one-half years after removal of a dysgerminoma followed by deep roentgen irradiation and male sex hormone therapy. A pulmonary lesion was first noted on a chest roentgenogram taken two and three-quarter years after operation for the primary tumor. The progress and growth of this lesion was followed for four years. Good palliation was obtained from the administration of testosterone proprionate over a two year period during which time the pulmonary metastasis slowly grew larger. Later, mediastinal involvement was demonstrated with invasion of the opposite lung. The lung metastases regressed less than 50 per cent following a series of deep roentgen treatments. Other metastases occurred in the supraclavicular, inguinal, abdominal, mediastinal, and retroperitoneal lymph glands, the kidneys, and the liver.—*Dysgerminoma: Case with pulmonary metastases; result of treatment with irradiation*

and male sex hormone, P. E. Russo & J. W. Kelso, Radiology, March, 1949, 52: 367.—(W. J. Steininger)

Massive Pleural Tumor.—Primary tumors of the pleura, either diffuse or localized, are the least common intrathoracic tumors. The diffuse tumor is the mesothelioma which is malignant and not resectable. Localized tumors arise from the subpleural connective tissue layers. Those on the parietal side often show a tendency toward infiltrative growth and metastases. Tumors arising from the visceral pleural surface include the sarcomas which may be pedunculated and show little tendency to infiltrate or to metastasize although they are considered sarcomatous. They are easily removed and cause death only because of the gigantic size to which they may grow. When small, such circumscribed tumors are diagnosed with difficulty, if at all, without exploration. Aspiration biopsy may aid. Bronchoscopy shows no lesion. A lobulated fibrosarcoma weighing 3,230 Gm. was successfully removed from a 52-year-old woman. Over two years she had gradually developed increasing dyspnea on exertion which culminated in severe orthopnea with congestive failure. A chest film taken ten years previously showed a lobulated density in the right lower lung field. Serial chest films showed gradual progressive enlargement of this density and at operation the encapsulated tumor nearly filled the entire hemithorax. The signs and symptoms of congestive failure due to mechanical encroachment upon the left auricle disappeared promptly after the tumor was removed. Follow-up examination nearly three years after removal showed the patient to be well and asymptomatic with no evidence of local recurrence of the neoplasm.—*Fibrosarcoma of the pleura mechanically causing congestive cardiac failure: Successful surgical removal, I. A. Sarot, Quart. Bull., Sea View Hosp., July, 1948, 10: 109.—(K. T. Bird)*

Hamartoma of Lung.—Hamartomas of the lung are tumor-like masses containing some or all of the normal histological elements which make up mature bronchi or lung tissue, quantitatively grouped in abnormal proportions so that one tissue element, usually cartilage, predominates. The tendency of hamartomas of the lung to undergo calcification or ossification is important from the roentgenological point of view. Large hamartomas which contain calcium or bone can be diagnosed with reasonable accuracy from roentgenograms alone. Small lesions which are of more common occurrence are more likely to simulate metastatic nodules or primary bronchogenic carcinomas and they cannot be diagnosed specifically from the roentgenograms. (Author's Summary)—*Roentgenologic significance of hamartoma of the lung, W. C. Hall, Am. J. Roentgenol., November, 1948, 60: 605.—(J. E. Farber)*

Gangrene from Grass.—Aspiration of timothy grass into the tracheobronchial tree is common. The grass is progressively propelled into the lung periphery; severe and prolonged complications may follow, including lung abscess, suppuration, bronchiectasis and, rarely, gangrene. A case is presented in which, for the first time, gangrene is reported as a sequel. An infant of 21 months swallowed some timothy hay, developed pulmonary suppuration, failed to respond to bronchoscopy and surgical drainage, and died 37 days after the onset. Autopsy demonstrated a diffuse purulent bronchitis, lung abscess of the right lower and middle lobes, and gangrene of the upper lobe.—*Pulmonary gangrene of a child following aspiration of timothy grass, D. J. Judge, E. C. Rice, & E. W. Davis, J. Pediat., January, 1949, 34: 87.—(W. H. Oatway, Jr.)*

Obstruction of Superior Vena Cava.—Of 250 cases of superior vena caval obstruction reported from 1904 to 1946, 145 were proved by autopsy or operation; the remainder were diagnosed on good clinical evidence. The thin-walled superior vena cava is easily compressible. Its close proximity to the aorta and tracheobronchial structures makes it

highly vulnerable to an extension of inflammatory or neoplastic processes from these areas. The right anterior mediastinal and right laterotracheal chains of lymph nodes are also intimately associated with this vein. Increased collateral circulation is an important consequence of caval obstruction and involves chiefly the internal mammary, vertebral, azygos, and lateral thoracic veins. Of 166 patients whose sex is reported, 79.5 per cent were men. The highest incidence is between the ages of 30 and 60 years. The three most common causes were malignant primary thoracic tumors (29.6 per cent), aortic aneurysms (24.0 per cent), and chronic fibrous mediastinitis (24.8 per cent). The latter includes tuberculosis, syphilis, and a group of diseases whose cause is unknown. From 1904 to 1946 the incidence of syphilitic mediastinitis in this series dropped from 28.6 to 0.9 per cent. In the nonspecific group of chronic fibrous mediastinitis it is probable that a trauma or respiratory infection leading to inflammation of the tracheobronchial lymph nodes plays a role. Since 1904, 19 cases of localized phlebitis with thrombus formation have been reported. The chief clinical manifestations of superior caval obstruction are evidence of the increased venous pressure in the regions drained by this vein and include edema of upper extremities, head and neck; cyanosis; dyspnea; headache; and chest pain. Hoarseness, dysphagia, and convulsions may be present. Diodrast visualization is valuable in revealing the site of obstruction but is rarely needed to make the diagnosis. Treatment is directed at the underlying disease. In chronic mediastinitis, mediastonotomy with release of any constrictive bands is indicated. Repeated phlebotomies may afford symptomatic relief. The prognosis varies with the underlying disease and some patients with good collateral circulation have survived for many years.—*Obstruction of the superior vena cava: A review of the literature and report of two personal cases, F. T. McIntire & E. M. Sykes, Jr., Ann. Int. Med., May, 1949, 39: 925.*—(*H. R. Nayer*)

Traumatic Bronchial Rupture.—Severe chest injuries may cause tears in the main stem bronchi at or close to the bifurcation of the trachea. When this occurs, the patient usually reveals shock, dyspnea, anoxia, interstitial emphysema, and cough. Whereas such accidents may cause death, patients have survived the immediate effects of their injury to develop posttraumatic bronchial occlusion with pulmonary collapse. Routine roentgenograms of the chest immediately after injury may reveal fractured ribs, interstitial emphysema, pneumothorax, pulmonary compression, and mediastinal shift. Later, when bronchial occlusion is complete, the classical roentgen manifestations of pulmonary collapse develop. Bronchograms reveal a cup-shaped blind pouch at the site of the occlusion. Substernal distress and dyspnea occur commonly in patients with posttraumatic bronchial occlusion. (Authors' summary.)—*Traumatic bronchial rupture with occlusion, P. J. Hodes, J. Johnson & J. P. Atkins, Am. J. Roentgenol., October, 1948, 60: 448.*—(*J. E. Farber*)

Angiocardiography of Great Vessels.—Conventional roentgen measurement of the great vessels is indirect, often inaccurate, and not well standardized. Angiocardiographic measurement of the great vessels is simple, accurate, and capable of standardization. The caliber of the ascending aortic arch gradually increases with age. It averaged in this series 28.6 mm. and ranged from 16 mm. to an upper limit of 38 mm. A simple and satisfactory evaluation of the pulmonary artery may be found in measurement of the right pulmonary artery in the frontal projection. In this series it averaged 23.4 mm. and ranged from 17 to an upper limit of 30 mm. It is anticipated that larger series of angiocardiographic measurements will supplement this preliminary report. (Authors' Summary)—*The angiocardiographic measurement of the normal great vessels, C. T. Dotter & I. Steinberg, Radiology, March, 1949, 52: 353.*—(*W. J. Steininger*)

Antimicrobial Therapy

Streptomycin in Tuberculous Enteritis.—Thirty-three cases of tuberculous enteritis were treated with streptomycin in a cooperative study involving 15 Veterans Administration hospitals. Intestinal symptoms had been present for an average of five months before streptomycin therapy. The mean known duration of the coexisting pulmonary disease was nineteen months. The daily intramuscular streptomycin dose varied between 1.0 and 2.0 Gm.; at the present time 1.0 Gm. is recommended in 2 doses. Nineteen patients completed courses of 60 to 120 days. Fourteen-day courses were used in 6 cases for symptomatic relief only. Eight cases are still under treatment. Oral treatment, 2 Gm. daily in 5 doses, was used in 2 patients for 66 and 120 days and in 3 patients for seven to fourteen days. Intramuscular streptomycin was uniformly effective in the relief of symptoms of tuberculous enteritis. Maximum subjective benefit was reached within one week in the majority of cases. Relief of diffused and localized tenderness, rigidity, and distention followed within a few days. With oral streptomycin four to six weeks of treatment were required for complete relief of symptoms. Intestinal symptoms recurred in 2 out of the 33 cases. A larger series and a longer follow-up will be necessary before the rate of remission can be established. Of the patients whose treatment had been completed, the average follow-up was six and one-half months. The roentgen-ray reports were summarized in 17 cases. All showed abnormalities before treatment. In 6 of this group the findings returned to normal after treatment. In 8 cases definite improvement was seen but some residual deformity remained. Two cases showed marked residual abnormality and one case developed signs of small bowel obstruction. A return to radiologic normalcy can be expected provided the abnormalities are primarily those of local irritation (*i.e.* spasm, hypermotility, loss of haustrations, mucosal irregularity, and others). Where ulceration has been deeper, more widespread, and of longer duration, and where lymphatic obstruction and interstitial inflammation have destroyed normal architecture of the bowel wall, radiologic changes may persist and there may be further distortion due to cicatricial contraction.—*Streptomycin in the treatment of tuberculous enteritis, a report of thirty-three cases, E. F. Mason, W. W. Kridelbaugh, W. H. Crouch & M. Ward, Am. J. M. Sc., January, 1949, 217: 28.*—(*W. J. Steininger*)

Streptomycin and Clotting Time.—The effect of streptomycin on the blood clotting and prothrombin times of 21 patients with pulmonary tuberculosis was studied by modifications of the Lee-White and Quick techniques. A closely parallel series of 21 phthisic patients served as a control. Each patient in the streptomycin group received 0.5 Gm. of streptomycin twice daily for 120 days. No correlation between the age, activity or extent of the tuberculosis and the clotting or prothrombin times was found in either the control or streptomycin groups. Two methods of investigation were used: (*1*) tests were made during the same hours on different days over a period of several weeks; (*2*) serial tests were performed prior to and at 15, 30, and 90 minutes following the injection of streptomycin or of distilled water. No significant effect upon the prothrombin time could be demonstrated by either method but the data suggests that streptomycin exerts an anticoagulant effect particularly at 90 minutes after injection. There is no evidence that the tuberculous process itself affects the behavior of the clotting and prothrombin times in response to streptomycin but this possibility was not excluded.—*Effect of streptomycin on blood-clotting time and prothrombin-time in man, L. Elson, Am. J. M. Sc., April, 1949, 217: 421.*—(*W. J. Steininger*)

Para-aminosalicylic Acid for Tuberculosis.—Ten patients with pulmonary tuberculosis were treated with para-aminosalicylic acid for periods of three months. They were all

young individuals with extensive bilateral progressive disease with toxic manifestations of the disease. At first the daily dosage was 5 Gm. every six hours. Later a weekly schedule was arranged of 30 Gm. daily for the first two days, 20 Gm. daily for the next four days, and no drug on the seventh day. All patients developed gastro-intestinal symptoms which varied in severity with the dosage of the drug. One patient developed a rash. In almost one-half of the cases, there was some clinical improvement but in no case was there complete clearing. Some patients had only a decrease in toxemia.—*Para-aminosalicylic acid, E. A. Joules & E. Nassau, Tubercle, May, 1949, 30: 98.*—(*A. G. Cohen*)

PAS for Bronchial and Urinary Tuberculosis.—The authors treated tuberculous tracheobronchitis and genito-urinary tuberculosis with para-aminosalicylic acid (PAS). Five patients who had extensive tracheobronchitis with ulceration and hyperplasia received a total dosage of 97 to 722 Gm. The daily dosage was between 12 and 15 Gm. given continuously or in interrupted courses of four days each. Symptoms decreased after treatment for seven to ten days and bronchoscopic improvement was observed after two to three weeks. In patients who had had previous streptomycin treatment with residual stenosis, a good result was achieved with PAS and dilatation. Tuberculosis of the genito-urinary tract was treated in 12 patients. The results were good in disease of the lower tract, tuberculous cystitis responding most readily. The kidney lesions were not influenced. One month of treatment was sufficient to allay the distressing dysuria and frequency in 9 of the 12 cases. Encouraging results were seen in certain cases of pulmonary tuberculosis; 20 of 40 patients with progressive lesions were markedly improved. Of these 20 patients, 15 had permanent loss of bacilli from the sputum. In 5 cases of pleurisy with effusion, no effect of PAS was demonstrable. In tuberculous meningitis a combination of streptomycin and PAS treatment was used with good results. In these cases PAS was given by a continuous duodenal drip of a 5 per cent solution in saline. It is felt that treatment with streptomycin and PAS simultaneously may give better results in the treatment of tuberculosis than when either drug is given alone.—*Die Therapie der Tuberkulose mit PAS (Paraaminosalicylsaüre) mit besonderer Berucksightigung der Bronchial under Nierentuberkulose, R. Hug, S. Moeschlin & E. Tanner, Schweiz. med. Wchnschr., April 23, 1949, 79: 353.*—(*H. Marcus*)

Infection after Pulmonary Resection.—From 1942 to 1947, 427 patients were subjected to pneumonectomy or lobectomy at the Massachusetts General Hospital. Sulphonamide drugs were used throughout this period and penicillin was introduced in 1944. During this interval, the use of tourniquet ligation of the hilar strictures was replaced more and more by individual ligation. Another technical advance was the careful suture of the bronchus and the capping of the closed stump with a pleural flap. Resection was performed for many diseases, particularly bronchiectasis, abscess, tuberculosis, and carcinoma. In six years, the gross mortality for pneumonectomy fell from 21.4 to 8.3 per cent and for lobectomy from 8.7 to 2.9 per cent. In 1947, there were no deaths from sepsis. In the first five years the empyema rate dropped from 21.4 to 3.7 per cent for pneumonectomy and from 27.7 to 2.0 per cent for lobectomy. In 1947, the rates were 21.7 and 1.5 per cent respectively. In 1944, one-half of the patients who died had empyema. Thereafter, this incidence gradually declined to zero. In cases of bronchiectasis, the patients are treated preoperatively with aerosol penicillin to which streptomycin sometimes is added. If empyema develops, daily aspiration and instillation of penicillin is often helpful; penicillin has hastened the cure of bronchopleural fistulae. Sulphonamide drugs reduced the empyema rate and penicillin did even better, but a combination of both is best. Each year, the length of hospital stay has gradually shortened. The preopera-

tive routine now is to give 100,000 units of penicillin every eight hours and 0.25 Gm. of streptomycin four times a day for two days. If fever is present, these may be given longer. If there is copious expectoration, 50,000 units of penicillin in one cc. of saline are given as aerosol four times a day; streptomycin may be added. Before closing the chest, 100,000 units of penicillin and 1.0 Gm. of streptomycin dissolved in 30 cc. of saline are left in the pleural cavity. The injection of both drugs is continued for five to six days.—*The occurrence of infection after pulmonary resection, C. C. Miller & R. H. Sweet, New England J. Med., April 14, 1949, 240: 589.*—(*A. G. Cohen*)

Laboratory Studies

Dubos Medium for Streptomycin Sensitivity Tests.—Tubercle bacilli were isolated from 140 tuberculous patients prior to treatment with streptomycin using egg slants and a Dubos albumin-Tween medium, the latter containing 10 units of penicillin per ml. Subcultures then were grown in tubes of Dubos medium containing various amounts of streptomycin. Cultures that grew on the Dubos-penicillin medium were planted directly into the tubes containing streptomycin. The egg cultures had to be subcultured in a Dubos broth before being used for the sensitivity tests. Of the 140 cultures 138 were sensitive to one unit or less of streptomycin, one to 2 units and one to 3 units. It is concluded that this Dubos medium is satisfactory for testing the streptomycin sensitivity of tubercle bacilli and that most strains isolated before treatment are highly sensitive to the drug.—*Value of Dubos medium in tests for streptomycin sensitivity of Mycobacterium tuberculosis, M. Mollov & A. Oshinsky, Am. J. Clin. Path., January 1949, 19: 67.*—(*J. S. Woolley*)

Kinetics of Benzoic Acid Oxidation.—The kinetics of the oxidation of benzoic acid by *Mycobacterium tuberculosis* BCG 8240 were analyzed. Six consecutive monomolecular reactions were postulated and the velocity constants given. Oxidation began with a latent period during which adaptive enzymes were formed. This latent period became shorter or vanished if the bacteria were treated previously with small amounts of benzoic acid. Enzymes gradually disappeared in the absence of benzoic acid. The effect of streptomycin was to depress equally all stages of oxidation. *The kinetics of the oxidation of benzoic acid by certain mycobacteria. G. S. Eadie, F. Bernheim, & R. J. Fitzgerald. J. Biol. Chem., November, 1948, 176: 857.*—(*F. B. Seibert*)

Bronchial Arteries in Bronchiectasis.—In the normal lung, anastomoses may occur between the two arterial systems but interarterial communications are more common in the presence of disease. A study of the bronchial arteries by Wood and Miller showed that frequent enlargement of these arteries and numerous large anastomoses with the pulmonary artery were present in subjects with tuberculosis. They also occurred in association with chronic passive congestion, Ayerza's disease, silicosis, emphysema, asthma, and "congenital cystic disease" of the lung. One instance in a case of bronchiectasis was mentioned. In the present study observations are reported on 18 specimens of lung removed surgically from patients with bronchiectasis and prepared as colored casts by the vinylite corrosion technique. In 15 of these specimens great enlargement of the bronchial arteries and numerous anastomoses of these vessels with the pulmonary arteries were observed. The communications were multiple and usually occurred in the walls of the bronchiectatic sacs of the fourth order or more distal branches of the segmental bronchi. In half of the specimens the anastomoses were 1.0 mm. or more in diameter. The enlargement of the bronchial vessels was associated with the development of granulation tissue during the pneumonitis that usually precedes bronchiectasis and with the increased metabolism of hypertrophied muscle and hyperplastic lymphoid tissue. The anastomoses may represent per-

sistent communicating channels originating in the granulation tissue which received vessels from both the bronchial and pulmonary arterial systems. The anastomoses are so large and numerous as to suggest that they have physiologic importance (*1*) in shunting pulmonary arterial blood away from the diseased tissue into relatively intact parenchyma where the pulmonary blood pressure is presumably lower, and (*2*) in producing hypertension in the pulmonary circulation.—*Enlargement of the bronchial arteries, and their anastomoses with the pulmonary arteries in bronchiectasis, A. A. Liebow, M. R. Hales & G. E. Lindskog, Am. J. Path., March, 1949, 25: 211.*—(*J. S. Woolley*)

Oil Pneumonia.—A controversy in the literature has occurred as the result of different observations on the effect of aspiration of peanut kernels, peanut extracts, and other peanut products. It has been shown that simple, neutral vegetable oils such as iodized sesame, poppyseed, and olive oils produce no reaction or injury to the lungs. In the present experiments peanut oil was introduced into the bronchial tree of rabbits. Lipid pneumonia was produced but it cleared in ten days leaving oil-containing macrophages. The phagocytes remained for ten weeks or more although no harm to the lung structure occurred. These results demonstrate the lack of a marked toxicity of peanut oil.—*Experimental peanut oil pneumonia in rabbits, W. G. Gobbel Jr., Am. J. Dis. Child., February, 1949, 77: 175.*—(*W. H. Oatway Jr.*)

Fluorescent Microscopy of Tubercle Bacilli.—Fluorescent microscopy, using the auramine stain for the detection of acid-fast bacilli, has not replaced the Ziehl-Neelsen technique as confidently predicted. Letters were addressed to the directors of 48 state health department laboratories and 39 replies were received. These replies revealed that only 24 laboratories had experimented with this method and in only 2 of these was it now being used routinely as superior to the conventional Ziehl-Neelsen technique. The present paper discusses the application of the method to sputum examination. If the lighting and staining (auramine) are satisfactory, thin smears from untreated specimens of sputum give optimum results, including good fluorescence, little interference, and few atypical bacilli or artefacts. A dark room is essential to reduce interfering outside light and minimize fatigue. The bacilli may be injured by mechanical handling of sputum and by chemicals or heat. Such injury introduces interfering fluorescence which tends to reduce or blur the sharp brilliance of the bacilli and to induce fatigue of the worker. This fatigue was the main reason given by the laboratory directors for discarding the method. Phenol introduces no undesirable effects and appears to be satisfactory as a storage or shipping medium for sputum. Cresol and Lysol, however, are unsatisfactory as shipping mediums, Cresol because it introduces interfering fluorescence, Lysol because of apparent dissolution of the bacillus, reduction in number of visible organisms, and alteration in morphology. Centrifugation increases the number of interfering fluorescent particles more than any other single factor tested.—*Limitations of fluorescent microscopy for detection of acid-fast bacilli, H. E. Lind, Am. J. Clin. Path., January 1949, 19: 72.*—(*J. S. Woolley*)

Public Health and Epidemiology

Overcrowding and Tuberculous Mortality.—Although the mortality from tuberculosis in the Netherlands is among the lowest in the world and is still falling, there is an alarming increase in the number of active cases reported in that country. The great post-war shortage of sanitarium beds has made it necessary to treat many infectious cases at home, but the severe housing shortage has increased the public health risk from each case so treated. Nearly 150,000 persons have no living quarters in regular dwellings. In

1947 the average number of persons per room was 4.5 in some regions; the national average was 0.9 per room. During the latter part of 1948, visits were made to 819 homes of tuberculous patients in five cities of various sizes to study the housing of such persons. Of the patients, 299 (37 per cent) were infectious and there were children under 16 years of age in 140 of the families of such patients. There was no separate room for 99 of the infectious persons and 72 did not have even a separate bed; 79 of the families lived "doubled up" with other families. A similar survey in Amsterdam during April, 1949, revealed that in 1,933 families, there were 2,046 patients with tubercle bacilli in the sputum and 351 persons with active tuberculosis but without detectable bacilli. These families included 6,094 adults and 1,667 children under the age of 15. Of the 2,046 infectious patients, 771 slept in separate beds but with other persons in the same room, 93 with children under 15 in the room. Another 303 patients slept with other persons in the same bed; another 126 slept in the family's living room. Of the 1,933 families, 269 lived "doubled up." The solution obviously must be the creation of more housing units and more sanitarium beds.—*Onderzoek naar de woningtoestanden van thuis verpleegde tuberculose-patiënten, die onder toezicht staan van de consultatiebureau's te Eindhoven, Den Haag, Maastricht, Nijmegen en Venray, A. E. G. de Vries Bruins, Tegen de Tuberculose, May–June, 1949, 45: 60.—(J. van der Vate)*

BCG for Students.—At the Cook County Hospital in Chicago 142 nursing students have been vaccinated with BCG since 1940; each had a normal chest roentgenogram and a negative reaction to 1 mg. of OT during her first week of training. None of this group has developed tuberculosis although they were allowed to work in the tuberculosis unit. A control group of 199 nonreactors who were not vaccinated was not allowed to have contact with known tuberculous patients but 3 of the group developed the disease. Three other cases developed during the same period among 286 nurses who reacted positively to tuberculin at the start of training. In a group of 109 medical students who were vaccinated at the University of Illinois since 1939, no case of tuberculosis has developed; 4 cases developed in the nonvaccinated group.—*BCG vaccination among medical and nursing students, E. E. Irons, Am. J. Dis. Child., March, 1949, 77: 376.—(W. H. Oatway Jr.)*

BCG Usage in Chicago.—The continuous study of BCG for 13 years in Chicago represents the longest project of its kind in the United States. It has shown BCG to be safe. From a group of newborn infants in a heavily infected environment, 1,417 were vaccinated and 1,414 were used as controls over a ten-year-period. Chest roentgenograms of the vaccinated group showed that 11 developed tuberculous lesions, and one child died; 39 lesions appeared in the nonvaccinated group and 7 deaths occurred. In a second group of infants from tuberculous households vaccinated and control infants were isolated in foster homes. Two lesions and no deaths occurred in the 151 vaccinated children; 5 lesions and 4 deaths occurred in the 105 controls. A third group was made up of children under 10 years of age, all living in a single housing project. Of these children 699 were vaccinated during a 5-year period; no case of tuberculosis developed. In 625 nonreacting alternately selected controls, there were 4 cases of the disease. Among 275 positive reactors in this third group, 2 lesions and one death occurred. It is suggested that only the portions of the population most likely to be infected be vaccinated. The most efficient approach is through schools and nurseries.—*BCG vaccination in Chicago, R. A. Black, Am. J. Dis. Child., March, 1949, 77: 381.—(W. H. Oatway Jr.)*

Mass Surveys.—Approximately 500,000 persons in Washington, D. C., were examined in a chest roentgenogram survey during 1948. Of this number, one per cent was found to

have definite tuberculosis and another 1.4 per cent had suspected tuberculosis. In addition, 1.4 per cent were thought to have cardiac or other abnormalities. More than 5,000 of the cases of definite tuberculosis were new; 83 to 85 per cent were minimal.—*Some medical and roentgenological aspects of mass chest surveys, A. C. Christie, Am. J. Roentgenol., February, 1949, 61: 147.*—(*J. E. Farber*)

Tuberculosis Among Students.—A continuous program of tuberculosis control has been conducted at the University of Pennsylvania where the average annual enrollment has been about 6,000. During the past fifteen years, 177 students were found to have pulmonary tuberculosis. In 1931, 48 per cent of the entering students were tuberculin-positive; in 1946 only 28 per cent were reactors in spite of the fact that the average age of the latter group was considerably higher. Of the 177 tuberculous students, 91 were medical students who comprised only 9 per cent of the total enrollment. The nonmedical students had an attack rate of 5.7 per 1,000. All tuberculous students were removed from school and readmitted only after the lesion was stabilized. Only 6 of the nonmedical students failed to be readmitted. The medical students had an attack rate of 39.6 per 1,000. Ten students entered medical school with lesions; 81 developed the disease during their course. There were also 5 students who developed serofibrinous pleurisy and were granted a year's leave of absence. Seniors accounted for 38.6 per cent of the new cases, juniors 49.1 per cent, and the sophomores 12.3 per cent. Most of the new lesions detected in the third year were found in the first few weeks of the school and there was a high rate of conversion from negative to positive tuberculin reactors during the second year. The teaching of physical diagnosis and pathology now has been modified to reduce contact with tuberculous patients and autopsy specimens. Among the medical students, the appearance of a parenchymal lesion of the reinfection type rarely followed closely upon a primary infection; this interval was less than a year in only one instance. Reinfection type lesions appeared more often in students who entered as tuberculin reactors than in those who entered as nonreactors. Four students developed lesions of the primary type; these appeared 6 to 8 months after the development of sensitivity to tuberculin.—*Tuberculosis among medical and academic students, H. D. Lees, Dis. of Chest, May, 1949, 15: 569.*—(*E. A. Rouff*)

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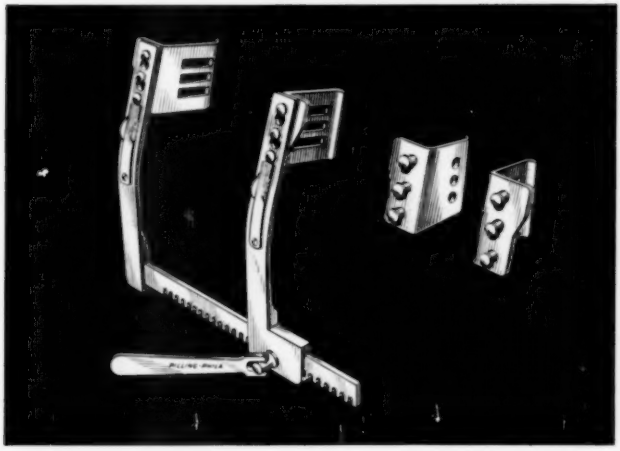

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